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TITLE: Efficacy of Adjunct Sleep Interventions for PTSD (EASI-PTSD)

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14. ABSTRACT

This is the final report for this study. We have completed all pre-and post assessment in all participants randomized to prazosin, placebo, or the behavioral sleep intervention. Two participants are currently completing the 4-month follow-up period. Data analysis for the acute treatment phase is currently underway, and the final analyses (which include 4-month follow-up data) will be initiated shortly. Recruitment has been more difficult than anticipated, but our enrollment rate (10% of individuals who completed the initial screening) is consistent with other ongoing studies in this population. Over the course of the performance period to date, this award has produced a numver of reportable outcomes, including several scientific, peer-review presentations and sumposia, and provided preliminary data for three successful applications for federal funding by the PI, Dr. Ger main.

15. SUBJECT TERMS
Sleep, PTSD, post-deployment adjustment disorders, prazosin, behavioral treatments of nightmares and insomnia.

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Efficacy of Adjunctive Sleep Interventions in PTSD (PR054093)
Final Progress Report
Progress Period: February 17, 2006 to March 16, 2010

I. INTRODUCTION.

Sleep disturbances are common and often resistant to first-line treatments of typical mental health disorders and post-deployment adjustment difficulties experienced by veterans who served in combat zones, including posttraumatic stress disorder. Although adjunctive pharmacological or behavioral sleep interventions are often required to adequately reduce nightmares and insomnia in veterans with these psychiatric difficulties, the efficacy and durability of adjunct sleep interventions have not been formally evaluated and compared. The overarching objective of this study was to investigate and compare the efficacy and durability of adjunctive sleep-focused interventions on sleep, daytime symptoms of PTSD, mood, and anxiety in male and female veterans who experience stress-related sleep disturbances. Preliminary analyses indicate significantly greater overall clinical improvements rated by participants and by clinicians over the course of the 8-week acute treatment phases in participants who randomized to the behavioral sleep intervention (BSI) condition compared to the prazosin and placebo conditions. These findings are promising, and suggest that that the two active interventions yield clinically meaningful improvements in sleep and daytime complaints. The findings to date also suggest that behavioral sleep intervention can yield larger sleep improvements relative to prazosin. However, some sleep improvements were observed in the placebo group, suggesting the close, weekly monitoring of sleep disturbances in a structured clinical context is associated with non-specific self-rated improvements in sleep. Follow-up data collection and final confirmatory analyses are underway. Of note, data collected from this award provided preliminary data for three federally-funded research grants. In addition, data collected in the baseline (pre-treatment) phase of the study provided preliminary findings to better interpret the anticipated final findings, as well as provide new directions for future research (Appendix E).

II. BODY.

Research accomplishments associated with each task outlined in the approved Statement of Work.
The tasks and timeline initially proposed and approved in the statement of work are provided in Table 1. Progress and outcomes on each of the tasks are described in detail below.

Table 1. Tasks timelines.

	Year 1			Year 2			Year 3			Year 4		
	Mo 1-4	Mo 5-8	Mo 9-12	Mo 1-4	Mo 5-8	Mo 9-12	Mo 1-4	Mo 5-8	Mo 9-12	Mo 1-4	Mo 5-8	Mo 9-12
Task												
Personnel Hiring & training												
Finalizing IRB approvals												
Advertisement development												
Order start-up supplies and material												
Subject recruitment & enrollment												
Randomization and treatment delivery												
Telephone Follow-ups												
Data safety and monitoring plan												
Preliminary data analysis and report												
Data analysis and report preparation												
Publications and final reports												

Task: Finalizing and renewing IRB approvals.

~~Approval at the University of Pittsburgh was originally granted January 13, 2006, and renewed yearly~~ afterwards. The protocol is now closed to enrollment, but remains open for data analysis. The current IRB approval letters are provided in the Appendix C.

Approval from the VA Pittsburgh Healthcare System (VAPHS) was originally granted on February 1, 2006 and renewing yearly. The protocol was suspended in December 2008. Our study was audited on December 18, 2008 by the Research Compliance Committee (RCC) of the VAPHS. The for-cause audit was set because of the deviation related to the initiation of medication treatment in a participant prior completion of the randomization process (see below, Event date: 10/24/2008). The auditors reviewed all 31 charts from participants recruited from VA-related recruitment efforts. The audit report is also provided here. The audit lead to the suspension of our study, because VA consent forms were not signed by a witness who is not affiliated with the research study. We had not implemented the signature of a witness other than the study staff members obtaining consents (coordinator and study physician) because of prior directive received by the VAPHS IRB board, indicating that only VA-credentialed staff members were allowed to have contact with VA-recruited participants, and that other staff members at the University should not have any contact with VA research participants. After the suspension of the study, and discussion with the VAPHS IRB and RCC, we have received directives that non-VA-credentialed individuals are now allowed to sign consent forms as witnesses, in addition to the study coordinator, study physician, and research participant. A more second audit found a number of non-VA compliant issues, such as protocol deviations regarding the use of actigraphy and missing blood draws for participants who were unable to complete these procedures while in the study. None of these issues endangered participants' safety or data integrity in the study. All were related to deviations or non-compliance issues with VA-specific IRB directives and requirements. All of these issues were resolved, but final reviews and approvals through all necessary VAPHS regulatory boards and channels span across a period of 10 months. The VAPHS Research Compliance Committee also required a change in PI, to from Dr. Germain to Dr. Eric Nofzinger. The process of credentialing and miscommunication between the VAPHS IRB and credentialing offices and Dr. Nofzinger exceeded the timeline for IRB renewal, so that the a full board review was required. Another change in PI-ship at the VAPHS was then made, from Dr. Nofzinger from Dr. Haas, consultant on this study and Co-Director of the VISN 4 MIRECC. All required documents were resubmitted full board IRB review in February 2010. During this time, data analysis using data collected from VA-recruited participants was prohibited. We finally received full IRB approval for data analysis only in May 2010 (see Appendix C). The current IRB approval letter is provided in the Appendix C.

Task: Subject recruitment and enrollment

Recruitment was extended relative to the original proposal, and completed at the University of Pittsburgh in March 2010.

Recruitment through the VAPHS posed several challenges over the performance period. The primary barrier encountered for recruitment relates to the initially target recruitment sites. We initially proposed to recruit veterans mostly from the local VA clinics by using advertisement posters and brochures, and via referral from VA clinicians at the local PTSD and OIF/OEF clinics. This strategy provided an average of 4 patients per month, which was clearly not sufficient, and below the expected 20 or more, based on estimates provided by our VA collaborators prior to the award proposal submission. Several meetings with referring clinicians and researchers at different VA clinics fail to increase recruitment referrals. Recruitment at the VA Pittsburgh Healthcare System (VAPHS) was closed in June 2009 due to lack of productivity for recruitment at that site. With the closure of the VAPHS recruitment site, we were able to redirect resources and personnel effort to focus on non-VA recruitment sources.

The recruitment flow chart provided in Appendix A provides a complete summary of recruitment and enrollment efforts for the duration of the award. Briefly, and since the initiation of recruitment in October 2006, we were contacted by 1531 veterans (526 in the last year of the performance period). We were able to reach and initiate the telephone screen with 1524, and to complete both the telephone script with 1097 individuals, and the telephone screening interview with 443. We were unable to complete the telephone screen with sixty-six other participants. All who passed the telephone screening interview were invited for a consent visit, but only 144 veterans came in person and completed the consent visit, and initiated screening procedures.

Demographic information for these 144 participants who provided informed, written consent is provided in Table 2.

Table 2. Enrollment as of 3/15/10
All participants

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	0	4	4
Not Hispanic or Latino	12	128	140
Ethnic Category Total of All Subjects*	12	132	144
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	34	36
White	10	97	107
Racial Categories: Total of All Subjects	**12**	**132**	**144**

Eight percent of consented veterans were women, and 25% were African Americans. The enrollment of women was lower than originally anticipated. The primary planned source of recruitment for women was the VAPHS Women's Health Clinic, but despite numerous attempts, we have not been able to successfully initiate recruitment at that site over the course of the performance period. Appendix B includes information about the distribution of by gender, race, and ethnicity for the three treatment groups, and demonstrated that randomization yield evenly distributed groups.

Although we exceed our recruitment plan, we did not fulfill the initial randomization goal of 90 veterans. As previously reported in prior reports, we encountered several difficulties in meeting the initial goal of screening up to 10 veterans per week primarily through referral from various clinics of the VAPHS. A series of administrative delays and incompatibilities, beyond the power of our research team, significantly impeded recruitment through VAPHS resources, despite sustained attempts to resolve these difficulties. Alternative sources of recruitment were put in place, including bus advertisements, radio and television advertisement, the development of a website (http://www.veteranssleep.pitt.edu), and online advertisements. In addition, the PI and research team sought active partnerships with local and regional military units, and community resources for veterans and their families, but these initiatives yielded few leads for research recruitment despite the development of growing collaborations with these bodies.

Randomization and treatment delivery

Of the 144 consented individuals, 58 passed all screening procedures, and 56 were randomized to one of the three treatment conditions (prazosin [18], placebo [16], or behavioral sleep intervention [19]). Three of the participants randomized to medications never initiated the treatment phase (out prior to meds in the flow chart).

No serious adverse events occurred over the duration of the study. Unanticipated events that occurred over the performance period between 2006 and 2010 are listed below:

From 2006 to 2007, no serious adverse events, adverse events, or unanticipated problems were reported.

From 2007 to 2008, the following unanticipated problems were reported:

1. On 11/21/2007, the study physician broke the blind before the research participant had completed the post-treatment questionnaire. This occurred because the sealed envelop with the randomization result was included with the documents provided to the study physician at the time of the participant's last post-assessment visit.

Although no harm was caused to the participant (who was randomized to placebo), it was determined that the randomization envelop should no longer by included in the participant's folder at the time of the last visit (or any other visit), and only retrieved from the locked file cabinet where they are stored after the completion of all post-treatment assessment.

~~***From 2008 to 2009, the following unanticipated problems were reported:***~~

1. On 6/10/2008, during the first wave of the mass mailing effort with the VAPHS, a veteran's widow received a recruitment letter addressed to her deceased husband. The widow returned a letter expressing dissatisfaction with the care received at the VA by her husband, to the VA MIRECC liaison, Liubomir Andrei Pisarov. The study coordinator and liaison contacted the VA patients' advocate, who contact the widow and offered help to address her concerns. Following this unanticipated event, the database created by the VA honest broken was revised and corrected to verify that no veteran for who a date of death is available is sent a recruitment letter.

2. On 10/24/2008, the study coordinator broke the blind with participant # 210640, who was completed the medication intervention sessions. Emergency notification card stated the participant was on the Placebo, but the randomization patient profile from the Pharmacy records indicated that the participant was actually randomized to and received prazosin, and was at 10mg at the end of the acute treatment phase. The participant did not experience any serious adverse event or unanticipated problem during her participation in the study. However, this unanticipated problem could have involved direct risk to the participant; and there was increased potential risk. Specifically, if risk if there had been a need to break the blind for medical reasons, especially if the study drug is known to have moderate to severe drug interactions, erroneous information would have been provided based on the emergency card labels.

The coordinator took the emergency card and the patient profile to the WPIC pharmacy, where he explained the discrepancy to one of the research pharmacists. The research pharmacist verified the randomization of the participant was indeed to prazosin, and not to placebo. He informed the study coordinator that at the randomization they review the study stratification criteria and log the participants name to the appropriate group (placebo or prazosin) on paper, they then enter the data electronically for the emergency contact cards (labels with the participants 10 and randomization). The pharmacist then provided a corrected emergency card to the coordinator. The participant was informed that she was on the medication and the coordinator completed the post intervention interview. The PI was informed shortly after of this incident. Emergency envelopes provided to the medical monitor (Dr. Jeffrey Peter), and study physicians (Dr, Eric Nofzinger Dr. Mammen) were immediately verified. All had the incorrect randomization information, i.e., indicated that the participant was on placebo, rather than on prazosin as it was the case. A meeting was held with the pharmacy manager (Karen Fielding) on the following business day. The problem arose in the process of the research pharmacist who makes the labels for the emergency cards, and looked at the wrong line on the randomization sheet. S/he did not verify that the subject's randomization and the information on the emergency cards matched. To avoid future occurrences, Mrs. Fielding had the research pharmacist pull the emergency envelopes from the WPIC ER file & verify all their contents. All envelopes were correct. They were matched to the participant's profile & the actual randomization sheet. This appears to be an isolated incident. She will also review this incident with her research staff. Appropriate reports were submitted and reviewed by the University of Pittsburgh and VAPHS IRB.

From 2009 to 20010, the following unanticipated problems were reported:

1. On January 10th 2009, an unanticipated deviation to the randomization protocol occurred when a participant initiated treatment in the medical arm of the study before the participant was actually randomized to the medication arms by our statistician. This was the result by misplacement of the randomization request in two participants who completed the baseline assessment concurrently. One participant had already been randomized (on 12/30/2008), and his randomization was mistakenly assigned to the other participant, who had not yet been randomized. The coordinator realized this mistake, immediately informed the PI and the VAPHS IRB. The randomization was completed on 1/13/2009. Both participants were indeed randomized to medications. This

deviation did not affect the risks to participants as both has completed the screening and baseline assessments, and were medically cleared. To ensure that this will incident will not occur again, we will now place larger labels on individual participants' binder to identify the randomization arm and date of randomization.

2. On February 1, 2010, an unanticipated even form was also submitted to the University IRB when a participant signed a consent form that our outdated. The error was captured rapidly, and the participant signed the latest consent again before continuing in the study.

Task: Telephone Follow-ups

One of the study participants still needs to complete the 4-month naturalistic follow-up period. The last assessment is scheduled for August 1, 2010.

Task: Data safety and monitoring plan

All study procedures, screening and evaluation findings, treatment delivery, integrity, outcomes, risks and adverse/unanticipated effects were closely monitored throughout the period of performance during weekly data and safety monitoring meetings and bi-yearly during the data safety and monitory board review.

The weekly meetings are also used to review, verify and achieve consensus on participants' eligibility and safety to participate in the study; verify if any member of team has become aware of the new information that alters the risk/benefit assessment of the present study, verify that confidentiality has been protected and no breach has occurred; and search the literature on new information that may affect the current assessment of the risk/benefit ratio. New literature relevant for the continuous assessment of the risks and benefits are the study is sought weekly, and reviewed when available.

A last Data and Safety Monitoring Board (DSMB) was held on April 9, 2010. The DSMB reviews were all conducted by Drs. Ellen Frank, Wesley Thompson, and Terry Keane. Summaries of recruitment results, study procedures, and any unexpected/adverse event were provided to the members for review. The DSMB expressed no concerns regarding the integrity of the data, participants' safety, and study procedures. The last and final DSMB report is included in the Appendix D.

Task 5. Preliminary and confirmation data analysis and report

Preliminary analyses included 46 veterans randomized to one of the three treatment conditions (15 BSI; 17 prazosin, 14 placebo). As shown in Table 3, the treatment groups did not differ at baseline on age, sex and race distribution, combat theater, baseline PTSD severity, use of psychotropic medications, psychiatric comorbidity, or combat exposure.

Table 3. Demographic for those randomized and initiated treatment

	BSI N=15	Prazosin N=17	Placebo N=14	Test Statistic Post Hoc
Age	37.4 (12.8)	38.3 (11.3)	43.6 (14.5)	F=0.97, df=2,43, p=0.39
%Male	80.0 (n=12)	88.2 (n=15)	100 (n=14)	Fisher Exact p=0.30
%Caucasian	66.7 (n=10)	82.4 (n=14)	92.9 (n=13)	Fisher Exact p=0.24
Combat Theater				Fisher Exact p=0.21
%Operation Iraqi Freedom	40.0 (n=6)	35.3 (n=6)	42.9 (n=6)	
%No conflict	20.0 (n=3)	5.9 (n=1)	21.4 (n=3)	
%Vietnam	6.7 (n=1)	0.0 (n=0)	21.4 (n=3)	
%Persian Gulf War	20.0 (n=3)	66.7 (n=6)	0.0 (n=0)	
%Operation Enduring Freedom	6.7 (n=1)	11.8 (n=2)	7.1 (n=1)	
%Bosnia	0.0 (n=0)	5.9 (n=1)	0.0 (n=0)	
%Korean Conflict	0.0 (n=0)	5.9 (n=1)	0.0 (n=0)	
%OIF/OEF	6.7 (n=1)	0.0 (n=0)	7.1 (n=0)	
CAPS	38.7 (22.5)	48.6 (23.6)	38.4 (18.5)	F=1.14, df=2,43, p=0.33
%on antidepressants, hypnotics, anti-anxiety meds or antipsychotics	33.3 (n=5)	47.1 (n=8)	42.9 (n=6)	Fisher Exact p=0.75

SCID Primary Diagnosis				Fisher Exact p=0.88
% Generalized anxiety disorder	0.0 (n=0)	5.9 (n=1)	0.0 (n=0)	
%Major depressive disorder, recurrent episode, unspecified	7.1 (n=1)	0.0 (n=0)	0.0 (n=0)	
%No Diagnosis on axis II,no diagnosis on or condition on axis I	7.1 (n=1)	5.9 (n=1)	7.1 (n=1)	
%Posttraumatic stress disorder	50.0 (n=7)	70.6 (n=12)	64.3 (n=9)	
%Primary Insomnia or Insomnia related to another disorder	35.7 (n=5)	17.7 (n=3)	28.6 (n=4)	
CES	10.9 (9.9) n=14	16.0 (10.1) n=16	19.5 (13.0) n=13	F=2.10, df=2,40, p=0.14

As shown in Figure 1, findings indicate significantly greater overall clinical improvements rated by participants and by clinicians over the course of the 8-week acute treatment phases in participants who randomized to the behavioral sleep intervention (BSI) condition compared to the prazosin and placebo condition ($F(2,235) = 6.49$, $p = .0018$; and $F(2,227) = 5.35$, $p = .0054$ respectively).

Changes in weekly sleep diary measures are presented in Figure 2. Weekly sleep diary measures also showed significant reductions in sleep latency in the BSI condition compared to placebo ($F(2,254) = 4.97$, $p = .0076$), and increased sleep efficiency compared to both prazosin and placebo ($F(2,253) = 14.94$, $p = .0001$). Wake time after sleep onset was also improved a trend levels over time in BSI condition relative to placebo ($p = .0581$). However, the number of dreams (nightmares or bad dreams) recalled over time did not differ across the three conditions.

Figure 1. Patient and clinician-rated global improvements

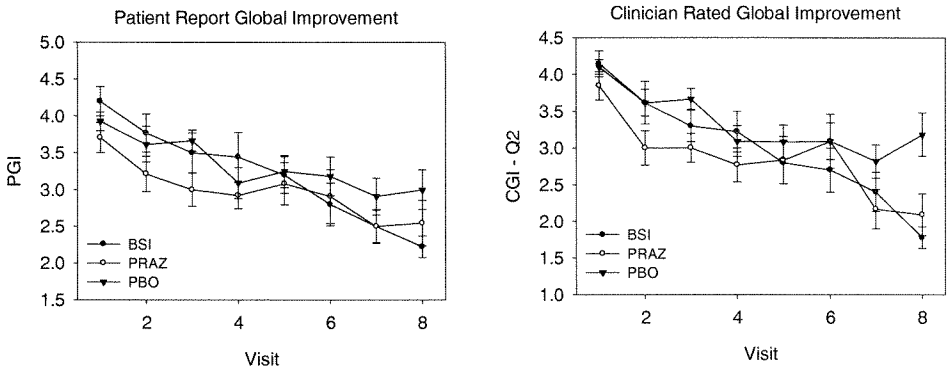


Figure 2. Changes in sleep diary measures across treatment conditions.

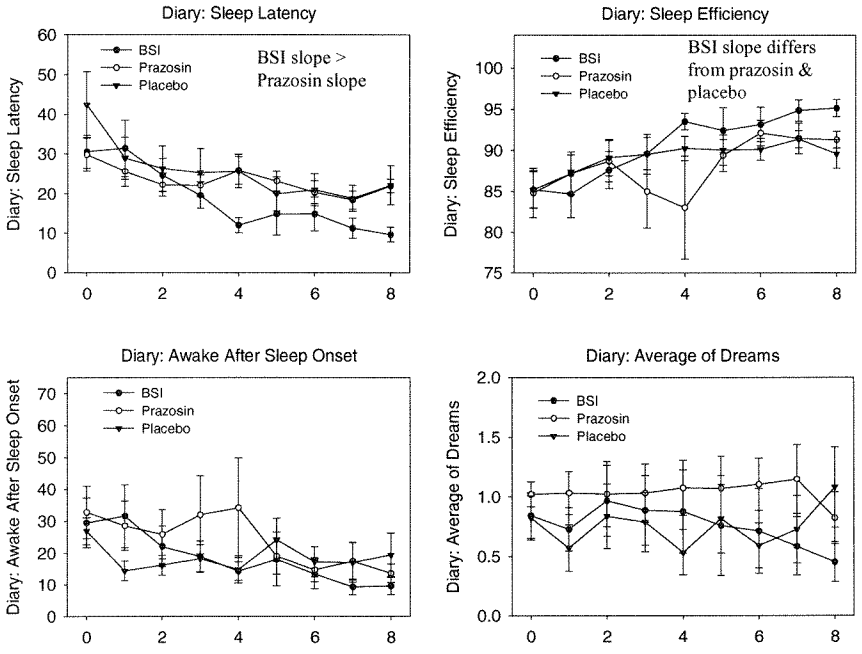
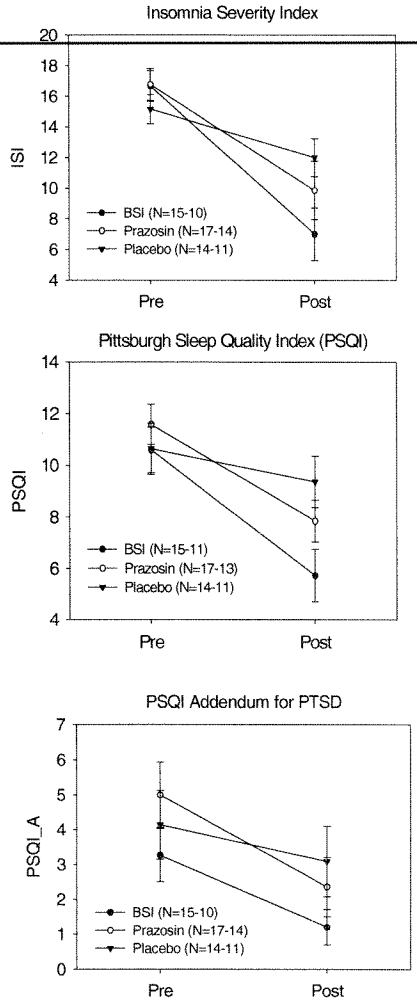


Figure 3a presents changes pre- and post-treatment on self-report measures of sleep and psychiatric symptoms. Insomnia severity was significantly improved in the BSI group compared to placebo. Other self-report sleep measures of sleep quality and disruptive nocturnal behaviors showed improvements over time in all three groups. Secondary outcome measures of psychiatric symptoms of PTSD (assessed with the Clinician-Administered PTSD Scale and PTSD Checklist), depression (assessed with the Beck Depression Inventory), and disability (assessed with the Sheehan Disability Scale) showed improvements over time in all groups, but the magnitude of changes was greater in the BSI and prazosin conditions compared to the placebo conditions (Figure 3b).

Figure 3a. Self-report sleep measures.



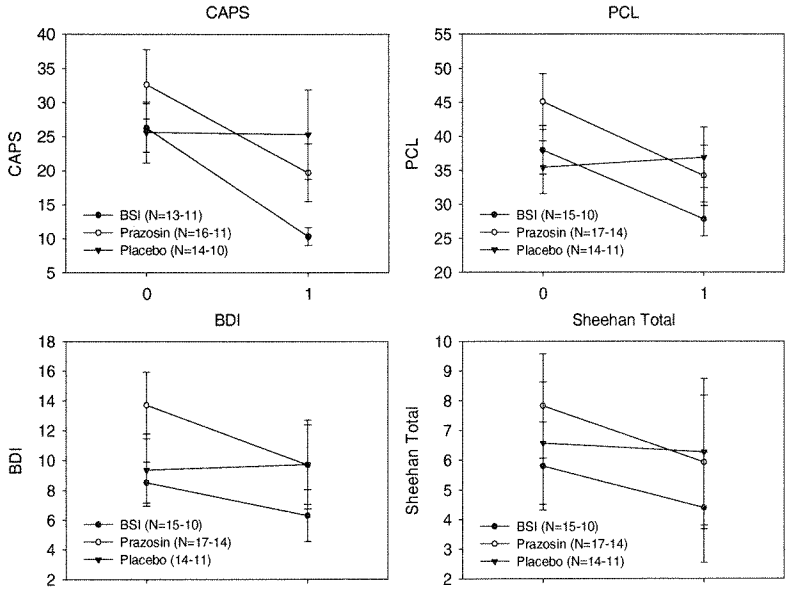
These findings are promising, and suggest that that the two active interventions yield clinically meaningful improvements in sleep and daytime complaints. However, some sleep improvements were observed in the placebo group, suggesting the close, weekly monitoring of sleep disturbances in a structured clinical context is associated with non-specific self-rated improvements in sleep. Follow-up data collection and final confirmatory analyses are underway.

Given the unique nature of the study, we plan to submit the primary outcome manuscript from this study to the *Journal of American Medical Association.* Reports on secondary outcomes will be submitted to other peer-review journals such as *SLEEP*, *Journal of Trauma Stress*, and *Psychosomatic Medicine.*

Problems in accomplishing any of the tasks.

Recruitment: We originally proposed to consent 120 participants, of whom 90 (75% retention) would be randomized and 66 were expected to complete the acute intervention phase (73% retention of randomized individuals). These retention rates were based on data collected in other sleep-focused, randomized clinical trials conducted by our colleagues in Pittsburgh. However, it has become obvious based on data acquired in the current study that previously collected data in clinical trials that enroll civilians do not generalized to clinical trials enrolling military veterans. As shown in the recruitment flow chart (Appendix A), the retention rate of consented individuals into randomization is 38.9 % (or 56 randomized / 144 consented). To enhance recruitment effort throughout the conduct of the

Figure 3b. Self-report measures of psychiatric symptoms and perceived disability.



study, we greatly intensified and diversified our recruitment efforts, by using television advertisements, bus advertisements, the study website, and initiated mass mailing efforts through the VAPHS. The latter was successful, but institutional differences beyond the control of the PI made recruitment through VA sources extremely difficult. In addition, the exclusion of veterans with comorbid medical conditions requiring the use of exclusionary medications (e.g., beta-blockers), or those who reported or showed significant symptoms of sleep apnea or substance misuse limited recruitment outcomes.

Despite the smaller sample size than anticipated, a recent report suggests that our sample size is sufficient to protect statistical power of the proposed analyses. A study by Sivertsen et al. (2006) compared cognitive-behavioral therapy for insomnia to eszopiclone, a benzodiazepine receptor agonist, in a sample of older adults with chronic primary insomnia, and showed that sample sizes of n = 17 were necessary to achieve 80% power at p = .05 for primary sleep outcomes measures derived from sleep diary and polysomnography (1). Our own original power estimates assumed treatment effect sizes of .6. Preliminary inspection of the data suggests that a effect sizes are detected in the two active treatment groups compared to placebo. Therefore, we are confident that we will be in an adequate position to obtain robust conclusions from the final analyses.

KEY RESEARCH ACCOMPLISHMENTS.

Key research accomplishments are detailed below under Reportable Outcomes. In addition, this study is unique research as it is the first to compare two active interventions, one behavioral and one pharmacological, targeting sleep disturbances in comparison to a placebo condition in a representative heterogeneous sample of military veterans. Preliminary findings suggest that both interventions are equally effective in improving sleep complaints, and are associated with improvements in daytime symptomatology of PTSD, depression, and perceived disability. Of note, participants randomized to the placebo condition also showed some improvements in sleep symptoms. We attribute these to the introduction of a more regular routine and heightened attention drawn on sleep brought by weekly appointment with the study physician and research coordinator, who performed the tasks using a patient-centered, collaboration medication management approach.

REPORTABLE OUTCOMES.

Several reportable outcomes have been derived from this award, and are listed below.

Peer-reviewed Manuscript:

- Germain A, Buysse DJ, Nofzinger EA. Sleep-specific Mechanisms Underlying Posttraumatic Stress Disorder: Integrative Review and Neurobiological Hypotheses. Sleep Medicine Reviews, 12(3):185-195, 2008. PMCID: PMC2490669
- Hasler BP, Germain A. Correlates and Treatments of Nightmares in Adults. Sleep Medicine Clinics, 4(4): 507-517, 2009. NIHMS163996

Invited Published Papers

- Germain A. Sleep Disturbances in Posttraumatic Stress Disorder (PTSD). Psychiatric Annals, 39(6):335-341, 2009.
- Germain A. Sleep and Dreams in Posttraumatic Stress Disorder. Frontiers in Neuroscience, Vol.3 (3):438, 2009.

Peer-Reviewed, Scientific Presentations at International Conferences:

The following research abstracts were submitted and accepted for presentation (oral or posters) at scientific meetings over the course of the award.

- Germain A, Nofzinger EA. *Efficacy of adjunctive sleep interventions in for PTSD*. Abstract presented at the 2006 DOD Military Health Research Forum, San Juan, Puerto Rico, May 2006.
- Stoll MT, Walsh CM, Troxel WM, Germain A. Frequency and effects of bereavement in OIF/OEF military veterans with PTSD. Poster to be presented at the 2008 National Conference for Undergraduate Research (NCUR), at Salisbury University, April 10-12, 2008.
- * Germain A., Walsh C, Stoll M, Hall M, & Buysse DJ. Objective Sleep Disturbances in Returning Veterans with PTSD: Preliminary Findings. Oral presentation given at the Sleep 2008, June 7-12, 2008, Baltimore, MD
- * Walsh C, Germain A, & Buysse DJ. Sleep quality and disturbances in Returning Veterans: Preliminary Comparisons with Primary Insomnia and Good Sleepers. Oral Presentation given at the Sleep 2008, June 7-12, 2008, Baltimore, MD
- * Germain A. & Buysse B. Brief Behavioral Treatment for Chronic Insomnia in Combat-Exposed Veterans: Preliminary Findings on Acceptability, Barriers to Adherence, and Outcomes. Oral presentation given at the 42nd Annual Convention of the Association for Behavioral and Cognitive Therapies (ABCT) held in Orlando. November 2008
- *Germain A., Walsh CM, & Buysse DJ. Objective and Subjective Sleep Disturbances in Returning Veterans: Preliminary Findings. Oral presented given at the 42nd Annual Convention of the Association for Behavioral and Cognitive Therapies (ABCT) held in Orlando. November 2008.
- *Germain A. *Nature and Behavioral Treatments of Sleep Disturbances in Military Veterans with Posttraumatic Stress Disorder*. In: G. Belleville (chair): Insomnia Comorbid with Medical and Mental Disorders: Nature, Impact, and Management. Symposium presentation presented at the Fourth Meeting of the Canadian Sleep Society, Toronto, ON, Canada. April 2009.
- Germain A, Raskind M., Ulmer C, and Edinger J, and Ross, R. Trauma and Sleep: Treatments and Health-Related Implications. Symposium presentation at the 2009 Sleep Meeting, June 2009. Seattle, WA.
- Russo M, Germain A, Baummann C, and Tucker DM. Sleep, Wake, and Traumatic Brain Injury. Symposium presentation at the 2009 Sleep Meeting, June 2009. Seattle, WA.
- *Germain A, Nofzinger EA. Efficacy of Sleep Intervention in Military Veterans with Post-Deployment Adjustment Disorders. Oral Presentation. Third Military Health Research Forum hosted by the Peer Reviewed Medical, Gulf War Illness, and psychological Health and Traumatic Brain Injury Research Program. Kansas City, MO. August 31 -September 3rd 2009.
- Germain A, Phillips M, Nofzinger EA. Neurobiology of sleep and sleep treatment response in returning veterans. Oral Presentation. Third Military Health Research Forum hosted by the Peer Reviewed Medical, Gulf War Illness, and psychological Health and Traumatic Brain Injury Research Program. Kansas City, MO. August 31 -September 3rd 2009.
- *Boudebesse C, Leboyer M, Begley A, Wood A, Miewald J, Hall M, Buysse DJ, Germain A. Actigraphic Sleep Measures in Military Veterans With PTSD And Insomnia. Abstract accepted for a poster presentation. Sleep, 33 (Suppl.), A235, 2010.
- *Germain A, Alman A, Cohen D, Cashmere D, Seres R, & Buysse DJ. Impact of Two Artifact Rejection Methods on REM Sleep Power Spectral Analysis. Abstract accepted for a poster presentation. Sleep, 33 (Suppl.) A356, 2010.
- *Cohen D, Alman J, Cashmere D, Miewald J, Germain A. Quantitative EEG analysis in REM sleep in OEF/OIF combat veterans with and without PTSD. Abstract accepted for a poster presentation. Sleep, 33 (Suppl.), A235, 2010.
- *Troxel W. & Germain A. Attachment anxiety is an independent correlate of slow-wave sleep in military veterans with post-traumatic stress disorder. Abstract submitted to the ABCT Convention. San Francisco, CA. November 2010.

* Denotes research abstract presented at national conferences, and provided in the Appendix.

Invited Lectures & Post-Graduate Courses:

- Germain A. *Sleep in War Veterans.* Invited Lecture. American Academy of Sleep Medicine Series Course: Current Topics in Sleep Medicine. Los Angeles, CA February 2009.
- Germain A. *Imagery Rehearsal, CBT, and Other Non-Drug Interventions for Nightmares and Parasomnias.* Invited Lecture. American Academy of Sleep Medicine Series Course: Evaluation and Management of Insomnia. Oak Brook, IL, March 2009.
- Germain A: *Face it or Fake it: Cognitive-Behavioral Treatments of Nightmares.* In: J. Edinger (Chair): A comprehensive overview of behavioral sleep medicine techniques: A nuts and bolts course for enhancing your sleep medicine practice): SLEEP 2009 Meeting Pre-Conference Graduate Course, June 7, 2009.
- Germain A. *Treating Insomnia Comorbid with PTSD.* In: R Manber (Chair) CBT for Insomnia Co-morbid w/Depressive & Anxiety. Course accepted at the 162nd American Psychiatric Association Annual Meeting, May 2009, San Francisco, CA.
- Germain A. *Brief Behavioral Treatment of Insomnia in Military Veterans.* Workshop presented at the Second Hidden Casualties of War Symposium sponsored by the UWF Center for Applied Psychology and the Naval Hospital Pensacola, May 2009.
- Germain A. *Treating Nightmares with Imagery Scripting and Rehearsal.* Workshop presented at the Second Hidden Casualties of War Symposium sponsored by the UWF Center for Applied Psychology and the Naval Hospital Pensacola, May 2009.
- Germain, A. *Sleep disturbances in PTSD.* Division of Psychiatry and Neuroscience, Behavioral Biology Department, Walter Reed Army Institute of Research. October 26, 2009. Invited Speaker.
- Germain A. *Brief Behavioral Treatment of Insomnia in Military Veterans.* Workshop presented at the Third Hidden Casualties of War Symposium sponsored by the UWF Center for Applied Psychology and the Naval Hospital Pensacola, May 2010.
- Germain A. *Treating Insomnia Comorbid with Anxiety Disorders.* In: R Manber (Chair) CBT for Insomnia Co-morbid w/Depressive & Anxiety. Course taught at the 163rd American Psychiatric Association Annual Meeting, May 2010, New Orleans, LA.
- Germain A. *When Nightmare and DreamStalker Invade Mindscape: Treatment of Nightmares.* A comprehensive overview of behavioral sleep medicine techniques. SLEEP 2010 Meeting Pre-Conference Graduate Course, June 5, 2010.
- Germain A. *PTSD: The Sleep Beast.* Invited workshop for the Sleep Research Society Trainee Day. SLEEP 2010, June 5, 2010.

Educational Presentations

The following presentations regarding the scientific and clinical rationale, design, and methods of our ongoing clinical trial were conducted by the PI over the award period. These presentations aimed 1) educating the scientific and clinical community involved in the care of military veterans with PTSD about the ongoing clinical trial; 2) promoting the importance of sleep in the re-adjustment process following redeployment to the USA in OIF/OEF service members; and 3) enhancing the visibility of the study to enhance recruitment.

- *Brief Behavioral Treatment of Insomnia in Military Veterans: A Pilot Study.* Multidisciplinary Sleep Conference, University of Pittsburgh, January 18, 2006.
- *Treatment of Nightmares Comorbid With Posttraumatic Stress Disorder (PTSD).* West Virginia University, Department of Behavioral Medicine and Psychiatry, Clinical Grand Rounds, Morgantown, WV, April 12, 2006.
- *Treating Sleep Disturbances in Military Veterans with PTSD.* Presentation at the Pittsburgh VA Brown Bag Lunch Seminar.
- *Efficacy of Adjunctive Sleep Interventions in PTSD.* Invited presentation for the VISN-4 MIRECC External Advisory Board, April 24, 2007.
- *Correlates and treatments of sleep disturbances in PTSD.* Young Investigator Lecture Series, Western Psychiatric Institute and Clinic, October 12, 2007.

- *Psychophysiological Correlates and Treatments of Sleep Disturbances in Post-traumatic Stress Disorder*. Friday, October 12, 2007. Young Investigator Lecture Series, Western Psychiatric Institute and Clinic.
- *PTSD and Sleep: What we do and why we do it.* Invited Staff Luncheon to the University of Pittsburgh Grants and Contracts Office and Office of Research. March 31, 2008.
- *A mouse model of sleep disturbances in PTSD: Concept Presentation.* Anne Germain, PhD. Multidisciplinary Sleep Conference, February 21, 2008.
- *Sleep and PTSD Research Program.* Anne Germain, Ph.D. CTSI Participant and Clinical Interactions Resources (PCIR) Overview, April 8, 2008 UPMC Montefiore Hospital.

Funding requested and obtained based on work supported by this award:

- **R34 MH080696**: *Brief Behavioral Treatment of Comorbid Insomnia in Returning Veterans*. The study aims at adapting and testing a brief behavioral treatment of insomnia. Recruitment data and clinical observations derived from this award provided preliminary data for this application. Role: PI.
- **R21MH083035:***Neurobiology of PTSD during REM sleep*. This study aims at exploring the neurobiological underpinnings of PTSD during REM sleep relative to wakefulness was recently funded. Recruitment data derived from the current clinical trial provided preliminary data for this application. Role: PI.

- **PT073961-W81XWH-07-PTSD-IIRA**: *Neurobiology of Sleep and Sleep Treatment Response*. This study will expand this award by including wake and sleep PET imaging prior and after treatment with prazosin or placebo to further investigate the mechanisms underlying sleep treatment response, and sleep specific, brain-based predictors of sleep treatment response. Role: PI.

Funding requested but not obtained:

Grant Title	Role	Funding Agency	Program
Vires Per Somnem: Enhancing Psychological Health through Sleep and Fatigue Management	PI	CDMRP	Psychological Health And Traumatic Brain Injury (PH/TBI) Research Program
A Randomized Controlled Trial of EMDR in Veterans with TBI and PTSD	Co-I	CDMRP	Psychological Health And Traumatic Brain Injury (PH/TBI) Research Program
Translational Studies of the Effects of Stress-Related Sleep Disruption on Learning and Memory	Co-I	Office of Naval Research	Multidisciplinary University Research Initiative
The role of sleep-dependent memory processes in the formation and maintenance of posttraumatic stress disorder (PTSD	Co-I	CDMRP	Psychological Health And Traumatic Brain Injury (PH/TBI) Research Program
Sleep resilience, comorbid anxiety, and treatment in a murine model of PTSD	Co-PI	(DMRDP)	Basic Research Award

Research training activities conducted under this award:

Undergraduate training:

- *Miriam Stoll*, University of Pittsburgh, Department of Psychology (September 2006 and April 2007). Research internship and directed readings. *Prevalence and severity of grief symptoms in OIF/OEF and Vietnam veterans.* Research findings were presented as a poster at the annual Psychology Research Day of the University of Pittsburgh (April 2007).
- *Ryan Stocker,* Slippery Rock University, Department of Psychology. Research Internship (May to August 2007). Literature review: Co-occurrence of PTSD and traumatic brain injury in military veterans. (Note: Mr. Stocker is an OIF veteran who joined Dr. Germain's staff as a research associate, after graduation. Since then, he been promoted gradually to the rank of research coordinator.)
- *Matthew Georg*, University of Pittsburgh, B.Sc. Psychology student. Research Internship (September 2008 to May 2009). *Differences in self-report vs. clinicians administered scales of psychiatric distress in returning veterans with PTSD: Relationships with military and demographic factors.*
- *Rebecca Smith*, University of Pittsburgh, B.Sc. Psychology and Statistics student (September 2008 to May 2009). *Nightmares and insomnia in Returning Veterans with PTSD*
- *Jennifer Alman*, Washington and Jefferson College, Neuroscience and biology major (May 2008 to June 2010). Research internship. *Fast frequency EEG activity in PTSD and insomnia, and neurobiological correlates during REM sleep. (Note:* Ms. Alman's research abstracts were awarded oral presentation at the national SLEEP meeting in 2009 and 2010. She also received a Merit Research Award from the Sleep Research Society for her work).

Medical Student Training:

- *Daniel Cohen*, University of Pittsburgh School of Medicine, MS-1. Summer Research Project (May to August 2009). *Quantitative EEG during REM sleep in combat-exposed military veterans with and without PTSD.*

Graduate Training

- *Jason Munsie, BA, Masters student in social work (September 2007-August 2007).* Mr. Munsie completed a research internship required as part of the Masters' Program in Social Work at the University of Pittsburgh with our research team under the close supervision of the PI. During his internship, Mr. Munsie assisted the research coordinator in maintaining SOPs and tracking recruitment and enrollment data. He completed extensive training in the assessment of sleep and psychiatric disorders.
- Elizabeth Shulby, BA, University of Pittsburgh, School of Social Work (September 2007 – August 2008). Research Internship: *Assessment of sleep disturbances in military veterans with PTSD.*
- Catharine Hebdon, BA, University of Pittsburgh, School of Social Work (September 2007 – August 2008).Research Internship: *Assessment of sleep disturbances in military veterans with PTSD.*
- *Carole Boudebesse, MD. 1st-year Master's Degree in Biology & Medical Sciences, Université Paris VI. (January 2009 to September 2009).* Master's Research Report: *Actigraphic measurements of sleep in bipolar disorder and PTSD.*

CONCLUSIONS

Recruitment of military veterans with this study has been challenging. Expert colleagues working in similar areas of clinical research (such as Drs. Terri Keane, Richard Ross, Wilfred Pigeon) as well as clinicians at local VA centers have corroborated our experience in difficulty retaining veterans, especially young veterans, in research studies.

Our preliminary findings suggest that the behavioral sleep intervention is associated with a slight advantage on overall improvements, prospective sleep diary measures of sleep latency and sleep efficiency, and symptoms of insomnia relative to prazosin and placebo. Our findings (albeit preliminary) are especially important given the growing number of findings suggesting that sleep disturbances are a modifiable risk factor of poor psychiatric outcomes, and that targeted treatments of sleep complaints can improve daytime functioning. Specifically,

sleep complaints are common among active and retired military personnel deployed to combat theaters. Difficulty staying asleep occurs in as many as 90% of combat veterans with posttraumatic stress disorder (PTSD), and in more than 62% of Vietnam veterans and Vietnam era veterans without PTSD (*2*). Sleep disturbance is endorsed by 6% to 30% of veterans involved in the first Gulf War (*3*), and longitudinal studies have shown that sleep disturbances do not spontaneously remit in a majority of military veterans (*4, 5*). Recent reports from samples of military veterans returning from Operations Enduring/Iraqi Freedom (OEF/OIF) are consistent with prior findings in cohorts of military veterans. Increased latency to fall asleep, increased duration of wakefulness after sleep onset, shortened sleep duration, and increased sleep fragmentation are common during military deployment (*6*). Sleep complaints are also one of the most common reasons for referral to mental health services during active duty (*7, 8*) post-deployment. In a recent study of returning veterans from Operations Enduring/Iraqi Freedom (OEF/OIF), 70% of those who endorsed clinically significant symptoms of insomnia also reported being interested in receiving help for sleep problems, and described sleep difficulties as socially acceptable in a military context (*9*). These findings contrast sharply with findings from Hoge and colleagues (*10*) showing that a minority of returning OEF/OIF veterans were interested in seeking and receiving behavioral health treatments for anxiety, mood, and substance disorders because of the potential for stigmatization associated with mental disorders. Of note, anxiety, mood, and substance disorders are all associated with clinically significant insomnia complaints (*11-16*).

These juxtaposed observations suggest that focusing on sleep disturbances as a treatment target in veterans, and especially in military veterans returning from recent and ongoing conflicts, may offer several advantages for the psychological care of military veterans. First, and because sleep disturbances are common and acceptable in a military culture, the perceived stigma for seeking help specifically for insomnia is likely to be lessened for military veterans before, during, and after military deployment. Thus, the treatment of insomnia may provide a non-stigmatizing entry into mental health care for military veterans. Second, growing evidence indicates that treatments targeting sleep disturbances that co-occurring with another physical or mental condition provide clinically meaningful improvements not only in sleep, but also marked gains in daytime function (*17-27*). Effective treatment of insomnia, for instance, is typically achieved relatively rapidly, within four to eight weeks, for a majority of insomnia patients (*24*) . Consequently, rapid improvements in sleep, mood, and daytime function may provide prompt positive reinforcement for help seeking behaviors, and can enhance patients' continuous engagement in treatment for comorbid conditions that are perceived as more stigmatizing, such as posttraumatic stress disorder or depression. In other words, the stigma associated with psychiatric services may be reduced as a byproduct of obtaining help and relief for sleep complaints. Third, alternative treatment approaches can rapidly be considered rapidly when the initial treatment does not yield the anticipated magnitude of improvements. Together, targeting sleep complaints as a primary target in military veterans may provide many opportunities to build therapeutic trust and rapport, while maximizing the likelihood of rapid therapeutic gains and encouraging healthier coping strategies for other, comorbid psychological difficulties. The findings to date derived from this study suggest that a behavioral sleep intervention, rather than a pharmacological approach, provided more robust improvements in sleep than prazosin in this representative and heterogeneous sample of military veterans. Interestingly, pharmacotherapy, rather than behavioral sleep treatment, are the primary treatment approach in military care settings (*8, e.g.,28, 29*).

Future studies should focus on understanding the mechanisms of treatment response, and individual predictors of sleep treatment response to behavioral and pharmacological approach. Efforts are also required in formatting and packing effective sleep focused interventions to heightened their military relevance and deployability in real-world contexts, including military operations and combat deployment. Finally, future studies should evaluate the impact of early detection of sleep complaints and early intervention on sleep and psychiatric outcomes, as well as on functional and physical health outcomes known to be impacted by poor sleep, including employability, fitness and readiness, cardiovascular diseases, metabolic diseases, and chronic pain.

Finally, this award has yielded several research abstracts and provided a unique platform to train junior clinical researchers, as listed in the reportable outcomes to date, and has provided unique and valuable preliminary data

for subsequent studies aimed at 1) developing novel intervention for military veterans who experience clinically significant sleep disturbances, and 2) further understanding the neurobiology of sleep and sleep treatment response in combat exposed veterans with and without PTSD.

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APPENDICES

A - Recruitment Flow Charts

B - Recruitment Demographic Information

C - IRB approval letters

D - Report from the Data Safety and Monitoring Board Meeting, April 9, 2010

E - Peer-Reviewed Papers and Research Abstracts

F- Personnel Covered on this Award

SUPPORTING DATA.
Supporting data are provided as relevant in the report.

APPENDIX A

RECRUITMENT FLOW CHART

EASIP FLOW REPORT

03/18/2010

Total Contacts 1531

- Not Interested: 7
- No Response: 427
- Not Eligible: 407
- Lost to Follow-up: 132

Interested 1524

Scripted 1097

Screened 443

Lost to Follow-up 66

Consented 144

Excluded at Screening 449

OTHER EXCLUSION	127
OTHER WITHDRAWN	53
NO LONGER OR NOT INTERESTED	36
USE OF ALPHA-1 ANTAGONIST OR BETA-BLOCKER	30
TOO BUSY / TIME COMMITMENT	26
POOR COMPLIANCE WITH STUDY PROCEDURES	25
OBSTRUCTIVE SLEEP APNEA	23
OTHER WITHDRAWAL	18
BIPOLAR DISORDER	16
PSYCHOTIC DISORDER	9
PROTOCOL BURDEN	8
AHI>15	8
SUBSTANCE ABUSE DISORDER	8
NO SLEEP COMPLAINT	7
INSUFFICIENT FINANCIAL COMPENSATION	7
CAPS SCORE > 80, DIAGNOSTIC INELIGIBILITY (DOES NOT MEET CRITERIA FOR PTSD)	6
FAMILY BURDEN	5
PSYCHOTROPIC OR NEUROLOGICAL MEDICATIONS AND/OR DOSAGE CHANGED IN PAST 2 MONTHS	5
OTHER MEDICAL ISSUES FROM PHYSICAL/LAB TESTS	4
HOSP FOR OR REQUIRED TREATMENT FOR SUICIDE IN PAST 6 MONTHS	4
TRAVEL TIME/DISTANCE	4
AGE (< 18 OR > 60)	3
SEVERE MAJOR DEPRESSIVE DISORDER	3
SCHEDULING DIFFICULTY	3
DOESN'T WANT TO DO A RESEARCH STUDY	3
CALLED TO ACTIVE DUTY	2
CHANGES IN SSRI'S OR OTHER MEDS	1
PREGNANT OR BREAST-FEEDING	1

Excluded prior to randomization 57

OTHER EXCLUSION	8
POOR COMPLIANCE WITH STUDY PROCEDURES	7
CAPS SCORE > 80, DIAGNOSTIC INELIGIBILITY (DOES NOT MEET CRITERIA FOR PTSD)	5
AHI>15	5
OTHER WITHDRAWN	5
NO LONGER OR NOT INTERESTED	4
OBSTRUCTIVE SLEEP APNEA	4
OTHER WITHDRAWAL	2
SUBSTANCE ABUSE DISORDER	2
HOSP FOR OR REQUIRED TREATMENT FOR SUICIDE IN PAST 6 MONTHS	2
TOO BUSY / TIME COMMITMENT	2
USE OF ALPHA-1 ANTAGONIST OR BETA-BLOCKER	1
SCHEDULING DIFFICULTY	1
SEVERE MAJOR DEPRESSIVE DISORDER	1
NO SLEEP COMPLAINT	1
INSUFFICIENT FINANCIAL COMPENSATION	1
CALLED TO ACTIVE DUTY	1
OTHER MEDICAL ISSUES FROM PHYSICAL/LAB TESTS	1

Passed Apnea Screen 58
Randomized 56
W/D Drop Out 2
Completed Baseline 54

GROUP 1: Blind to Medication 0

GROUP 5: Out Prior to Meds 3

GROUP BSI: n = 19

INTERVENTION: W/D Drop Out	6
INTERVENTION: Completed	11
FOLLOW UP: W/D Drop Out	0
FOLLOW UP: Completed	11
POST FOLLOW UP: W/D Drop Out	2
POST FOLLOW UP: Active	0
COMPLETED PROTOCOL	10

GROUP PLACEBO: n = 16

INTERVENTION: W/D Drop Out	4
INTERVENTION: Completed	12
FOLLOW UP: W/D Drop Out	0
FOLLOW UP: Completed	12
POST FOLLOW UP: W/D Drop Out	0
POST FOLLOW UP: Active	0
COMPLETED PROTOCOL	11

GROUP PRAZOSIN: n = 18

INTERVENTION: W/D Drop Out	5
INTERVENTION: Completed	13
FOLLOW UP: W/D Drop Out	0
FOLLOW UP: Completed	13
POST FOLLOW UP: W/D Drop Out	1
POST FOLLOW UP: Active	1
COMPLETED PROTOCOL	11

APPENDIX B

RECRUITMENT DEMOGRAPHIC INFORMATION

Table 2. Enrollment as of 3/15/10 All participants			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	4	4
Not Hispanic or Latino	12	128	140
Ethnic Category Total of All Subjects*	12	132	144
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	34	36
White	10	97	107
Racial Categories: Total of All Subjects	**12**	**132**	**144**

Table Enrollment as of 3/15/10 BSI Participants			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	0	0
Not Hispanic or Latino	4	15	19
Ethnic Category Total of All Subjects*	4	15	19
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	3	4
White	3	11	14
Racial Categories: Total of All Subjects	**4**	**15**	**19**

Table Enrollment as of 3/15/10 Placebo Participants			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	0	0
Not Hispanic or Latino	1	15	16
Ethnic Category Total of All Subjects*	1	15	16
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	1	14	15
Racial Categories: Total of All Subjects	**1**	**15**	**16**

Table Enrollment as of 3/15/10 Prazosin Participants			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	0	15	17
Ethnic Category Total of All Subjects*	2	16	18
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	3	3
White	2	13	15
Racial Categories: Total of All Subjects	**2**	**16**	**18**

APPENDIX C

IRB APPROVAL LETTERS

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Anne Germain, PhD

From: Robert Sweet, MD, Vice Chair

Date: 3/24/2010

IRB#: REN10020016 / IRB0510050

Subject: Efficacy of Sleep Interventions for Post Deployment Stress Disorders or PDSD

At its full board meeting on 3/16/2010, the University of Pittsburgh Institutional Review Board,Committee C, reviewed the Renewal for the above referenced research study and approved it pending minor modifications. Your responses to these comments have been reviewed and the research submission, in its currently modified form, adequately addresses the concerns of the IRB and is therefore approved.

The risk level designation is Greater Than Minimal Risk

Approval Date: 3/24/2010
Expiration Date: 3/15/2011

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. The IRB Reference Manual (Chapter 3, Section 3.3) describes the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

Institutional Review Board (IRB)
VA Pittsburgh Healthcare System #646
7180 Highland Drive • Pittsburgh, PA 15206

IRB APPROVAL - Continuing Review

Date: May 16, 2010
From: Bruce S. Ling, M.D., M.P.H.
Investigator: Gretchen Haas, Ph.D.
Protocol: Efficacy of Adjunct Sleep Interventions for PTSD
ID: 02386 Prom#: N/A Protocol#: N/A

The following items were reviewed and approved through Expedited Review:

- Research Protocol (03/05/2010)
- Abstract (03/03/2010)
- Amendment - PI Change to Dr. Haas: Protocol (03/03/2010)
- Conflict of Interest - Barry Fisher-no conflicts (03/08/2010)
- Conflict of Interest - Jeffrey Peters-conflict identified (03/05/2010)
- Conflict of Interest - Steven Forman-conflict identified (03/05/2010)
- Conflict of Interest - Gretchen Haas-conflict identified (03/03/2010)
- Conflict of Interest - Liubomir Andrei Pisarov-no conflicts (03/03/2010)
- Conflict of Interest - Oommen Mammen-no conflicts (03/02/2010)
- Conflict of Interest - Robin Richardson-no conflicts (03/02/2010)
- Conflict of Interest - Ryan Stocker-no conflicts (03/01/2010)
- Conflict of Interest - Anne Germain-no conflicts (02/28/2010)
- Continuing Review (03/03/2010)
- Request for Expedited Continuing Review (03/03/2010)
- Memo from Dr. Haas accepting PI role (03/01/2010)
- Memo from Dr. Nofzinger requesting Dr. Haas as PI (03/01/2010)
- RCC Memo (10/13/2009)
- Data Safety Monitoring Board Summary (04/09/2010)
- Data Safety Monitoring Board Summary (07/22/2009)
- Data Safety Monitoring Board Summary (01/21/2009)
- Data Safety Monitoring Board Summary (07/11/2008)
- Approved Off-Site Storage/Transfer of Data Request (09/10/2009)

Expedited Approval was granted on 05/16/2010 for a period of 12 months and will expire on 05/15/2011. Your Continuing Review is scheduled for 03/28/2011. This Expedited review will be reported to the fully convened Institutional Review Board (IRB) on 06/28/2010.

This request for continuing review was reviewed and approved by the IRB Chairman/Designee under the following expedited continuing review category:

Category 8: Continuing review of research previously approved by the convened IRB as follows:
a. where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
b. where no subjects have been enrolled and no additional risks have been identified; or
c. where the remaining research activities are limited to data analysis.

If the study involves the use of Informed Consent Forms:
A copy of each subject's signed informed consent form must be submitted to the VAPHS Research Compliance Officer within 24 hours of signature. Copies must be hand delivered to Highland Drive, Building 2, Room 2074W or faxed to 412-954-5385.

Risk Assessment: Greater than Minimal; IRB Level of Scrutiny: Low (The risk assessment was made considering Social; Physical; Psychological; and Economic Risk).

Medical Records of subjects entered into this study must be FLAGGED

AE Reporting Level: AE2
AE2 - All serious AEs that are possibly related and all unanticipated but not serious AEs that are at least possibly related to the study procedures need to be reported to the IRB using the current adverse event reporting form. AEs that are not study related should not be reported.

Data Security Level:
Level 2 – VA Sensitive information is collected/used and subjects have given permission for the use/disclosure

Approval by each of the following is required prior to study continuation:
Institutional Review Board (IRB)
Institutional Biosafety Committee (IBC)

Approval for study continuation is contingent upon your compliance with the requirements of the Research Service for the conduct of studies involving human subjects.

Bruce S. Ling, M.D., M.P.H.

Please answer all questions:

1.	Did all research participants give informed consent?		Yes	No
1a.	If No, did this project receive a waiver of documentation of informed consent?		Yes	No
2.	Did you make any changes to the consent form that were not reviewed and approved by the IRB?	N/A	Yes	No
3.	Have there been any changes regarding use of vulnerable populations (mentally challenged, prisoners, inpatients who receive long-term care for chronic illness, terminally ill, pregnant women, children, employees, or students)?		Yes	No
4.	Were there any unanticipated risks or new information discovered during the course of the study that might affect participants' willingness to participate?		Yes	No
4a.	If Yes, did you submit a revised informed consent form to the IRB for review and approval?	N/A	Yes	No
4b.	If Yes, were participants re-consented?	N/A	Yes	No
4c.	If Yes, were participants notified in writing? Please provide a copy of the notification if you have not already done so.	N/A	Yes	No
5.	Were all Serious Adverse Events and Safety Report notifications reported to the IRB?	N/A	Yes	No
6.	Were all amendments submitted to the IRB?	N/A	Yes	No
7.	Were all unanticipated protocol deviations (including errors and accidents) reported to the IRB?	N/A	Yes	No
8.	Were all advertisements submitted to the IRB?	N/A	Yes	No
9.	Is participant enrollment continuing?		Yes	No
9a.	If Yes, how long will enrollments continue?			
9b.	How many more participants are anticipated?			
10.	Is participant enrollment permanently closed?		Yes	No
11.	Are participants being seen for follow-up?		Yes	No
11a.	If Yes, how long will participants be followed?			
12.	Is the research project completed?		Yes	No
13.	Would you like to terminate the project?		Yes	No
14.	Have there been any changes, since the last report, with respect to the source (or the sufficiency) of funding, the need for space, the need for equipment and supplies, and/or the personnel involved? If Yes, please summarize the changes on the back.		Yes	No

Signature: _____ Date: 3/03/2010

(ONLY THE PRINCIPAL INVESTIGATOR IS AUTHORIZED TO SIGN)

APPROVED **DISAPPROVED**

Signature: _____ Date: 3/16/10

Chairperson, Institutional Review Board (IRB)

Department of Veterans Affairs **REPORT OF SUBCOMMITTEE ON HUMAN STUDIES**

MIRB # 02386

Project/Program Title: Efficacy of Adjunct Sleep Interventions for PTSD

Principal Investigator: Gretchen Haas, PhD

VAMC: VA Pittsburgh Healthcare System (646) Review Date: 5/16/2010

Amendment dated

COMMITTEE FINDINGS:

1. The information given in the Informed Consent under the Description of Research by Investigator is complete, accurate, and understandable to a research subject or surrogate who possesses standard reading and comprehension skills. ☒ YES ☐ NO

2. The informed consent is obtained by the principal investigator or a trained and supervised designate under suitable circumstances. ☒ YES ☐ NO

3. Every effort has been made to decrease risk to subject(s)? ☒ YES ☐ NO

4. The potential research benefits justify the risk to subject(s)? ☒ YES ☐ NO

5. If subject is incompetent and surrogate consent is obtained, have all of the following conditions been met: a) the research can't be done on competent subjects; b) there is no risk to the subject, or if risk exists the direct benefit to subject is substantially greater; c) If an incompetent subject resist, he/she will not have to participate; d) If there exists any question about the subject's competency, the basis for decision on competency has been fully described. ☒ YES ☐ NO

6. If the subject is paid, the payment is reasonable and commensurate with the subject's contribution ☒ YES ☐ NO ☐ NA

7. Members of minority groups and women have been included in the study population whenever possible and scientifically desirable. ☒ YES ☐ NO

8. Comments: (Indicate if Expedited Review) This study is approved for the period of _5/16/2010__to_5/15/2011__. Extension beyond_5/15/2011__requires reapproval of the SHS and the Research Office.

☒ EXPEDITED

RECOMMENDATION: ☒ APPROVED ☐ DISAPPROVE/REVISE

SIGNATURE OF CHAIRMAN DATE 5/16/2010

Bruce Ling, MD, MPH, IRB Chairman

VA FORM OCT 1995 **10-1223**

APPENDIX D

DATA AND SAFETY MONITORING BOARD

APPRIL 9, 2010

FINAL REPORT

UNIVERSITY of CALIFORNIA, SAN DIEGO
HEALTH SCIENCES
SAM and ROSE STEIN INSTITUTE for RESEARCH ON AGING
9500 Gilman Drive, La Jolla, CA 92093-0664
(858) 534-4020 phone
(858) 534-5475 fax

Pittsburgh, April 9, 2010

Meeting minutes, Data Safety and Monitoring Board (DSMB)
Efficacy of Adjunct Sleep Interventions for Post-Deployment Stress Disorders (PDSD)
DSMB Members: Drs. Wesley Thompson, Ph.D. (Chair), Ellen Frank, Ph.D., and Terrence Keane, MD

1. **Review of progress since last DSMB meeting in July 2009**
   a. Investigator's change: Dr. Nofzinger is on entrepreneurial leave, but continues to be actively involved as an external consultant on the study.
   b. Recruitment/Enrollment Data: We have now established an advertisement strategy that optimizes the return on investment for public advertisements.

   The study recruitment flow charts for the entire period of performance and for the period since the last DSMB review were provided to the committee members for their review. Consistent with other randomized controlled trials, approximately 10% of the people who complete a telephone script (description of the study), complete the telephone screening, and are invited for a consent visit. About 50% of those consented are then lost due to exclusionary criteria, or are lost during the screening process. Overall, about 4% of people who initially contact us to inquire about the research study are consented and completed all study procedures.

   c. Safety issues: There has been no safety issue in the last 6 months of the period of performance. There has been one unanticipated event reported to the IRB in the last six months. This event relate to the use of a consent form that did not include the latest modifications regarding personnel. The error was detected immediately, and the participant signed the updated consent form at the subsequent visit.

      - University of Pittsburgh: Modification to Research Protocol and Consent Forms: Modifications made to the protocol and consent form related mainly to updating the study staff, and new television advertisement. The more important modification made to the protocol and consent related to procedures to determine the need to lower the medication dosage during the weekly medication monitoring visit. Specifically, the procedures stated that a drop in $\geq$ 10 mmHg would require the lowering the prazosin to the lower dosage level, regardless of the presence of symptoms of hypotension. After careful review of the literature and consultation with Dr Marroquin, expert cardiologist consultant on the study, and with Dr. Murray Raskind who has had extensive experience with the use and safety of prazosin in military veterans, we have modify the protocol and consent to indicate that

drops ≥ 10mmHG *associated with symptoms of hypotension* would require to lowering of the prazosin dose.

- The study was renewed at the University of Pittsburgh IRB on 3/24/2010 until 3/15/2011.

VAPHS IRB: The study was submitted for renewal to the VAPHS in September 2009. Because of a combination of delays incurred in the scheduled IRB meetings, miscommunication with Dr Eric Nofzinger, who served as the PI at the VAPHS site, and incomplete training provided by Dr. Nofzinger, the VAPHS IRB was unable to obtain all necessary trainings to approve the study as submitted for review. Dr. Gretchen Haas, who served as the VA liaison on the study, agreed to take over the PI-ship of the study, and will now serve as the VAPHS PI. Modifications to the protocol were submitted in February 2010. We are now awaiting review. The protocol had been closed to recruitment at the VAPHS in June 2009, but will remain open for data analysis upon approval by the IRB,

Of note, Dr. Keane specified that as long as the data collected from VA participants would be used for data analysis, the protocol should remain open at the VA, even after the set data has been de-identified.

1. **Discussion of recruitment/enrollment efforts**
   a. Recruitment Flow Chart:
      - One issue discussed relates to the large number of exclusion for "other" reasons. This group includes participants who were excluded due to other blood pressure medications or if who had other serious medical issues precluding their participation in the study.
   b. Targeted vs. current enrollment figure
      - Our original estimation was that we would need to consent up to 100 participants to be able to meet the enrollment goals of 30 subjects by treatment arm. Power estimates indicated that we need to detect effect on the primary outcome measures. The final enrollment is 16 placebo, 18 Prazosin, and 19 BSI. Recruitment has been extremely difficult for this study.
   c. The termination of study enrollment occurred on March 16, 2010. The study remains open for data analysis at the University.
   d. Data analysis status
      - We will keep protocol open at the VA to use data from 9 participants originally recruited through the VA. This protocol will be closed once the primary manuscript is accepted for publication. Given certification and training requirements at the VA, it will not be possible to keep the study open longer at no additional costs to our research program.

3. **Discussion of adverse events, deviations, and unanticipated events**
   a. One unanticipated event has been reported to the University IRB in the lat performance period. The consent form used was not the most current edition. This was promptly identified and corrected.

4. ***Discussion among DSMB members regarding specific recommendations to be made and approval to continue***
   - **The committee inquired about possible venues for publications of the study results.** JAMA, Journal of Traumatic Stress, Biological Psychiatry, Sleep Journals should be considered. Other journals such as Depression and Anxiety Disorders, and Behavior Therapy are also suggested. The report should reach the audience most likely to be interested in the outcome, namely, clinicians working with veterans.

5. **Recommendations.**

- Members of the DSMB reviewed and approved the last period of performance. There was no issue noted with safety, data integrity, and monitoring plan.
- The investigators can initiate preliminary and confirmatory data analysis.
- The members agreed that no further review is requested.

DSMB Committee Chair

4/19/10
Date

Wesley K. Thompson, Ph.D.
Assistant Professor in Residence
University of California, San Diego
Director of Statistics
Stein Institute for Research on Aging

APPENDIX E

PEER-REVIEWED PAPERS AND RESEARCH ABSTRACTS

Sleep Medicine Reviews (2008) 12, 185–195

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THEORETICAL REVIEW

Sleep-specific mechanisms underlying posttraumatic stress disorder: Integrative review and neurobiological hypotheses

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KEYWORDS
Posttraumatic stress disorder;
Sleep;
Arousal;
Amygdala;
Medial prefrontal cortex;
Insomnia;
Nightmares

Summary *Posttraumatic stress disorder* (PTSD) is a prevalent disorder that is associated with poor clinical and health outcomes, and considerable health care utilization and costs. Recent estimates suggest that 5–20% of military personnel who serve in current conflicts in Iraq and Afghanistan meet diagnostic criteria for PTSD. Clinically, sleep disturbances are core features of PTSD that are often resistant to first-line treatments, independently contribute to poor daytime functioning, and often require sleep-focused treatments. Physiologically, these observations suggest that PTSD is partially mediated by sleep disruption and its neurobiological correlates that are not adequately addressed by first-line treatments. However, polysomnographic studies have provided limited insights into the neurobiological underpinnings of PTSD during sleep. There is an urgent need to apply state-of-the-science sleep measurement methods to bridge the apparent gap between the clinical significance of sleep disturbances in PTSD and the limited understanding of their neurobiological underpinnings. Here, we propose an integrative review of findings derived from neurobiological models of fear conditioning and fear extinction, PTSD, and sleep–wake regulation, suggesting that the amygdala and medial prefrontal cortex can directly contribute to sleep disturbances in PTSD. Testable hypotheses regarding the neurobiological underpinnings of PTSD across the sleep–wake cycle are offered.

Introduction

Posttraumatic stress disorder (PTSD) is a clinical syndrome characterized by re-experiencing, avoidance, and hyperarousal reactions that persist for more than 1 month after exposure to a traumatic event. Violent crimes, including rape and physical assaults, combat exposure, and natural disasters constitute examples of traumatic events that can involve threat to integrity of the self or others and can be accompanied by intense fear, helplessness, or horror.[1] Trauma exposure is not a rare

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event: more than two-thirds of the general population is exposed to at least one traumatic event over their lifetime.[2] Epidemiological studies indicate that community prevalence estimates of PTSD range from 1% to 10%,[2,3] with higher estimates reported in victims of interpersonal violence (20–30%)[2–4] and combat veterans (15–30%).[5] In veterans of the current Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF), Hoge et al.[6] found that 31% of OEF service members and 71–86% of OIF service members reported multiple combat experiences, and as many as one out of nine troops returning from Afghanistan, and one out of six troops returning from Iraq endorse clinically significant PTSD symptoms.[6] These estimates are likely to rise over time, based on a recent report that indicates that 33.4% of OIF/OEF returnees evaluated at VA Healthcare facilities between 2002 and 2006 met diagnostic criteria for mental disorders, including PTSD.[7] PTSD is often a chronic condition, and is associated with enormous health care costs in both military and civilian samples.[8] Recommended first-line treatments for PTSD include selective serotonin reuptake inhibitors (SSRIs), and cognitive–behavioral approaches such as exposure-based and cognitive therapy.[9,10]

There is growing evidence that sleep disruption that occurs following trauma exposure may constitute a specific mechanism involved in the pathophysiology of chronic PTSD and poor clinical outcomes. Subjective and objective sleep disturbances occurring early after trauma exposure, as well as heightened sympathovagal tone during REM sleep, are associated with an increased risk of meeting criteria for PTSD at subsequent assessments conducted up to 1 year later.[11–13] Sleep disturbances are a core feature of PTSD. Nightmares and insomnia are diagnostic symptoms of PTSD,[1] and other sleep disturbances such as sleep avoidance, sleep terrors, nocturnal anxiety attacks, simple and complex motor behaviors and vocalizations, acting out dreams, sleep apnea, and periodic leg movement disorders are also frequently reported and observed by PTSD patients.[14,15] Additionally, sleep disturbances independently exacerbate daytime symptoms, and contribute to poor clinical outcomes in PTSD, such as increased severity of depression,[16] suicidality,[16] and general psychiatric distress,[17] poorer quality of life and functioning,[17] and poorer perceived physical health,[18] and increased alcohol and drug use.[19,20] While these associations between sleep disturbances and poor clinical outcomes are derived from a posteriori observations, they stress the need for prospectively monitoring the possible development of sleep disturbances in trauma-exposed individuals, and the role of sleep disturbances as mediators of the relationship between PTSD and clinical outcomes. Finally, sleep disturbances are often resistant to recommended first-line interventions.[21,22] Adjunctive sleep-focused pharmacological or behavioral interventions are commonly used to alleviate PTSD-related nightmares and insomnia. Of note, the use of benzodiazepines remains highly common in PTSD, possibly for alleviating daytime anxiety symptoms and sleep disturbances, despite the absence of evidence supporting their efficacy.[25,26] Effective treatments of nightmares and insomnia also associated with improvements in daytime PTSD symptoms, depression, quality of life, and perceived physical health (e.g.,[23,24,27] see also Ref.[4] for review). Together, these observations raise the possibilities that (1) trauma exposure directly alters sleep–wake regulation mechanisms, (2) PTSD is partially mediated by sleep-specific mechanisms, and (3) normalization of altered neurobiological mechanisms underlying sleep disturbances in PTSD requires targeted treatments.

The overarching goal of this paper is to integrate convergent lines of evidence derived from sleep neuroimaging studies in related disorders, from waking neuroimaging studies conducted on PTSD patients, and from animal models of fear conditioning to provide a preliminary model and testable hypotheses of the neurobiological underpinnings of PTSD during rapid-eye movement (REM) and non-REM (NREM) sleep. Prior sleep findings in PTSD samples are only briefly reviewed here. Extensive critical review of prior qualitative and polysomnographic studies of sleep in PTSD samples and review of pharmacological and behavioral treatments that target PTSD-related sleep disturbances are available elsewhere.[28–30] Findings derived from sleep neuroimaging studies in healthy human subjects are then briefly reviewed. Because the hyperactivity of the amygdala and impaired function of the medial frontal cortex are neurobiological correlates of PTSD, animal and human studies suggesting that the amygdala and medial prefrontal cortex directly influence the regulation and/or expression of REM and NREM sleep are highlighted. The neurobiology of fear conditioning and fear extinction, complementary animal models of PTSD in humans, their effects on sleep, as well as neuroimaging findings observed in PTSD samples are also presented. Findings from these areas of research evidence potentially significant dual roles of the amygdala and medial prefrontal cortex as both critical structures involved in the fear response and PTSD, and important modulator of NREM and REM sleep.

Based on these observations, preliminary models and hypotheses regarding potential neurobiological correlates of PTSD during NREM and REM sleep are described.

An in-depth understanding of the sleep-specific underpinnings of PTSD, acquired with state-of-the-science measurement methods, is essential to guide for development, refinement, and testing of innovative prevention and interventions strategies across the sleep–wake cycle. More broadly, better empirically derived models of PTSD during sleep may generate novel insights into the pathophysiology, prevention, and treatment of other adjustment and stress-related disorders, such as those affecting cohorts of combat-exposed military veterans, as well as of victims of violent crimes and terrorist attacks, and survivors of natural disasters. Finally, elucidating the neurobiological underpinnings of PTSD during sleep can inform efforts to identify the mechanisms subserving resistance of sleep disturbances to first-line treatments of PTSD, as well as the distinct mechanisms underlying treatment response to sleep treatments in PTSD, and other stress-related disorders.

Sleep neuroimaging findings in healthy human subjects

Consistent with animal models of sleep regulation, sleep neuroimaging studies in healthy humans indicate that specific patterns of neuronal activation and deactivation characterize NREM and REM sleep relative to wakefulness. Specifically, whole-brain glucose metabolism and blood flow are reduced by 30–40% during NREM sleep in healthy subjects relative to wakefulness.[31] NREM sleep is also associated with relative reduced metabolic activity and blood flow in the wake-promoting areas including the pontine and midbrain reticular formation and thalamus, as well as in associative cortices.[31,32] A relative increase in neuronal activity in regions involved in the generation and maintenance of sleep, such as the dorsal pontine tegmentum and basal forebrain has also been observed.[31] Some studies have reported reduced activity of paralimbic cortices, including the anterior cingulate gyrus and parahippocampal gyrus during NREM sleep relative to wakefulness, whereas others have not.[31] Braun et al.[32] suggested that this disengagement of paralimbic structures and isolation of limbic structures (e.g., amygdala, hippocampus) from other heteromodal cortices may facilitate the restorative function of NREM sleep.[31,32] The pattern of neuronal deactivation observed in NREM sleep relative to wakefulness suggests that NREM is an endogenous state of attenuated arousal.

During REM sleep, whole-brain glucose metabolism is increased by 16% relative to NREM sleep, and non-significantly different from wakefulness levels.[32] REM sleep is characterized by increased regional cerebral metabolic activity and blood flow in the amygdala and anterior paralimbic areas, and with increased activity in the medial pons and thalamus relative to wakefulness.[32–34] Lateral prefrontal cortices, parietal cortices, and primary sensory cortices are further deactivated relative to wakefulness and NREM sleep during REM sleep. These selective activation and deactivation patterns during REM sleep relative to wakefulness in healthy subjects have yielded the hypothesis that dreams may reflect the mental representations of high limbic activations in conjunctions with deactivation of high-order cortical regions.[34] The pattern of activation observed during REM sleep suggests that REM sleep is an endogenous state of heightened activity in emotional arousal brain centers.

The amygdala and medial prefrontal cortex as modulators of REM sleep and NREM sleep

It is clear from animal studies that limbic and paralimbic regions are not among the primary regulators of NREM and REM sleep.[35–38] However, sleep neuroimaging studies in humans have shown that neuronal activity in amygdala and anterior paralimbic cortices including the medial prefrontal cortex varies across the sleep wake cycle. Although the amygdala and medial prefrontal cortex are not primary brain sites involved in the regulation of sleep *per se*, growing evidence suggests that both regions are important modulators of NREM and REM sleep.

Neuronal firing in the amygdala varies across the sleep–wake cycle, with higher firing rates during wakefulness and REM sleep compared to NREM sleep. In healthy human subjects, neuronal activity in the amygdala remains unchanged or is slightly reduced during NREM sleep relative to wakefulness,[31,32,39] and is considerably increased during REM sleep compared to both NREM sleep and wakefulness. The amygdala shares interconnections with the basal forebrain, hypothalamus, preoptic area of the anterior hypothalamus, brainstem reticular formation, and solitary tract nucleus. It also shares reciprocal connections with the REM-on and REM-off centers. Thus, the amygdala

is anatomically positioned to influence sleep via its connection to wakefulness-promoting and sleep-promoting areas. Stimulation of the amygdala during REM sleep increases PGO waves in REM and NREM sleep,[40] whereas inactivation of the amygdala with tetrodotoxin decreases sleep latency, and increases slow-wave activity during wakefulness, REM sleep, and NREM sleep.[41,42] Lesions of the amygdala in rhesus monkeys are associated with increased sleep consolidation and total sleep time, and sleep consolidation is proportional to lesion size.[43]

The medial prefrontal cortex, and especially the orbitofrontal cortex (OFC), influence sleep, and more specifically NREM sleep. Anatomically, the OFC has afferent and efferent connections with sleep-promoting regions, including the solitary tract nucleus and the ventrolateral preoptic area (VLPOA). Electrical stimulation of the OFC produces EEG synchrony and behavioral sleep, whereas lesions and ablation of the OFC are associated with reduced slow-wave sleep and reductions in behavioral sleep (see Ref.[35] for review). Neurons of the subgenual cingulate cortex, another region of the medial frontal cortex, increase their firing rate during NREM sleep in rhesus monkeys.[44]

The role of the amygdala and of the medial prefrontal cortex in modulating REM and NREM sleep in humans remains incompletely explored. However, and as described below, functional and structural abnormalities of the amygdala and medial prefrontal cortex that are suspected to subserve the pathophysiology of PTSD may also directly affect NREM and REM sleep regulation via interconnections between the amygdala, medial frontal cortex, and sleep- and arousal-promoting brain regions.

Neurobiological correlates of fear conditioning, fear extinction, and PTSD

Pavlovian fear conditioning and fear extinction paradigms have been proposed as animal models of PTSD.[45] Fear conditioning arises when a neutral stimulus (e.g., light, tone) closely precedes in time the occurrence of an aversive, emotionally significant event (e.g., shock) that will elicit a fear response (e.g., freezing). The neutral stimulus is termed the conditioned stimulus (CS), and the aversive event is termed the unconditioned stimulus (UCS). With repetition of the association, the neutral stimulus (CS) alone can elicit the fear response, now termed as the conditioned response (CR). With repeated presentation of the CS alone, the conditioned fear response is attenuated and eliminated. This process is called extinction.

During acquisition of fear conditioning, sensory information is transmitted to the lateral amygdala via sensory cortices and thalamus. Information is then transmitted from the lateral amygdala to the central nucleus of the amygdala, which sends projections to hypothalamic and brainstem regions that subserve autonomic and visceral fear responses. Rodent models of fear conditioning, using single-cell and multiunit recordings, c-fos activity, electrical or pharmacological stimulation, lesions, or temporary deactivation methods have shown that the amygdala and medial prefrontal cortex play critical roles in both the acquisition of fear conditioning and in fear extinction (see Ref.[46] for review). Extinction does not replace or erase the fear CR, but rather reflects new learning, which competes with the CR. Recall of fear extinction relies heavily on an intact infralimbic cortex in animals,[47] which corresponds to the rostral anterior cingulate cortex, medial OFC, and subcallosal cortex (including the subgenual cingulate cortex) in humans. In healthy human subjects, functional neuroimaging studies have confirmed the role of the amygdala in fear conditioning (e.g., Refs.[48,49]), as well as in fear extinction, and increased activation of the medial prefrontal cortex during fear extinction training and during fear extinction recall.[50]

Functional neuroimaging findings in PTSD patients are also consistent with animal models and preclinical studies of fear conditioning and fear extinction in humans. Specifically, waking brain imaging studies indicate that PTSD is characterized by hyper-responsiveness of the amygdala to threat-related stimuli,[51–56] and/or blunted responsiveness of the medial prefrontal cortex, which exerts inhibitory control over the amygdala.[57,58] Altered perfusion in limbic and frontal regions has also been observed in the absence of trauma reminders. Reduced volume of the anterior cingulate has been reported in PTSD subjects compared to non-PTSD subjects.[59,60] Thus, reduced functional activity and reduced volume of the ventromedial prefrontal cortex may both yield reduced inhibition of hyperresponsive amygdala in PTSD. Medication-free PTSD subjects show increased fear conditioning and deficits in fear extinction compared to non-PTSD subjects,[61] as well as increased amygdalar activation during fear conditioning, and attenuated activation of the medial prefrontal cortex during extinction compared to non-PTSD subjects.[62]

Effects of fear conditioning and PTSD on sleep

Animal studies have investigated the acute effects of fear conditioning on sleep as a model of the

physiological underpinnings of sleep in PTSD. While this model does not closely reflect the persistence of sleep disturbances long after exposure to the original trauma seen in human PTSD, it nevertheless provides insights into the effects of fear conditioning on sleep and their physiological substrates. In rats and mice, fear conditioning increases REM sleep latency, decreases REM sleep duration[63–65] and number of REM bouts,[66] and increases ponto-geniculo-occipital (PGO) waves, a marker of alerting mechanisms during sleep and wakefulness analogous to REMs in humans.[63,65] Alternatively, safety conditioning, where animals learn that they will not be exposed to aversive stimuli in a given environment or given a specific cue never paired with the aversive stimulus, is associated with increased REM sleep duration and percent.[66]

The effects of cued fear conditioning on sleep in animals are mediated by amygdala projections to brainstem regions involved in alerting and REM sleep generation.[65] In addition, the effects of fear conditioning on sleep appear to be related to heightened neuronal activity of the brainstem reticular activating system during sleep. In mice, fear conditioning is associated with increased c-fos expression in amygdala, locus coeruleus, and dorsal raphe nucleus, but not in the pontopedunculopontine tegmentum (PPT), and laterodorsal tegmentum (LDT).[67] The sustained and increased neural activity of amygdala, the locus coeruleus (LC), and dorsal raphe during sleep after fear conditioning disrupts REM sleep, via maintained inhibition of the cholinergic activity responsible for REM sleep generation by increased activity of the LC and dorsal raphe nucleus.

There are no studies on the effects of fear extinction on sleep in animal models. However, the relationship between sleep and fear extinction is highlighted by the effects of sleep deprivation on fear extinction in rats and mice. Specifically, sleep deprivation impairs the acquisition of fear extinction.[68] Given that fear extinction relies heavily on an intact medial prefrontal cortex, it seems plausible that sleep deprivation impairs fear extinction via its effects on the prefrontal cortex. In an analogous manner, chronic sleep disruption in PTSD interferes with fear extinction by further impairing or exacerbating impairments of the medial prefrontal cortex.

No study has yet investigated the neurobiological correlates of the effects of fear conditioning or fear extinction on NREM and REM sleep in humans. Multiple polysomnographic studies that compared PTSD and non-PTSD samples have been conducted. Overall, there are discrepancies regarding the presence and nature of objective sleep disturbance. Some PSG studies in PTSD patients have reported REM sleep anomalies, e.g.,[69–74], whereas other did not, e.g.,[75–77] NREM sleep anomalies such as reduced slow-wave sleep have also been reported in some.[75] A recent meta-analysis found small to medium effect sizes for increased REM density and increased percentage of stage 1 sleep, and reduced slow-wave sleep in PTSD compared to non-PTSD groups.[78] It has been hypothesized that REM sleep and NREM sleep mechanisms can underlie the production of posttraumatic nightmares, and contribute to the pathogenesis and maintenance of PTSD.[12,72,79] Heightened activity of REM sleep regulation centers and of the amygdala during sleep have also been suggested as neurobiological correlates of REM sleep anomalies in PTSD subjects.[79–81] Consistent with Revonsuo's hypothesis that a function of dreaming is threat simulation and rehearsal of motor patterns involved in escaping threats,[82] heightened activation of the amygdala may also subserve in the occurrence of PTSD- and non-PTSD-related nightmares.[81] However, the neurobiological correlates of REM sleep and NREM sleep in PTSD, as well as the neurobiological correlates of PTSD-related nightmares remain unexplored.

In summary, the amygdala and the medial prefrontal cortex are involved in the neurobiology of PTSD and of the effects of fear conditioning on sleep in animals, in addition to the role they play in modulation of NREM and REM sleep. Heightened amygdala activity, and/or impaired medial prefrontal cortex function observed in PTSD patients may adversely affect the regulation of NREM and REM sleep via their interconnections with arousal- and sleep-promoting brain. Both REM sleep and NREM sleep are disrupted in PTSD, but the neurobiology of these sleep disturbances in PTSD have not been elucidated by polysomnographic studies.

Neurobiological hypotheses of PTSD during sleep

The study of the neurobiological correlates of PTSD during NREM and REM sleep offers a unique paradigm to observe natural activation and deactivation patterns in endogenous states of attenuated central arousal and heightened limbic activity, respectively.

To further the prior hypothesis that sleep mechanisms contribute to the pathophysiology of PTSD, we propose that REM sleep amplifies altered function of the amygdala and medial frontal cortex in PTSD patients; amplification of

abnormal amygdala activation in combination with reduced activation of the medial prefrontal cortex could subserve nightmares. Figure 1a depicts a preliminary model regarding neurobiological correlates of REM sleep in PTSD subjects compared to healthy subjects, and relative to wakefulness. It is first hypothesized that heightened amygdala activity (Figure 1b) and blunted increase in activity of the medial prefrontal cortex (Figure 1c) characterize PTSD subjects compared to non-PTSD healthy subjects during REM sleep. These changes have direct impact on brainstem REM sleep regulation mechanisms, such as increased activity of brainstem REM-off regions (Figure 1d; LC, raphe), and attenuated activity of the brainstem REM-on nuclei (Figure 1e) PPT/LDG). Persistent activity of the LC

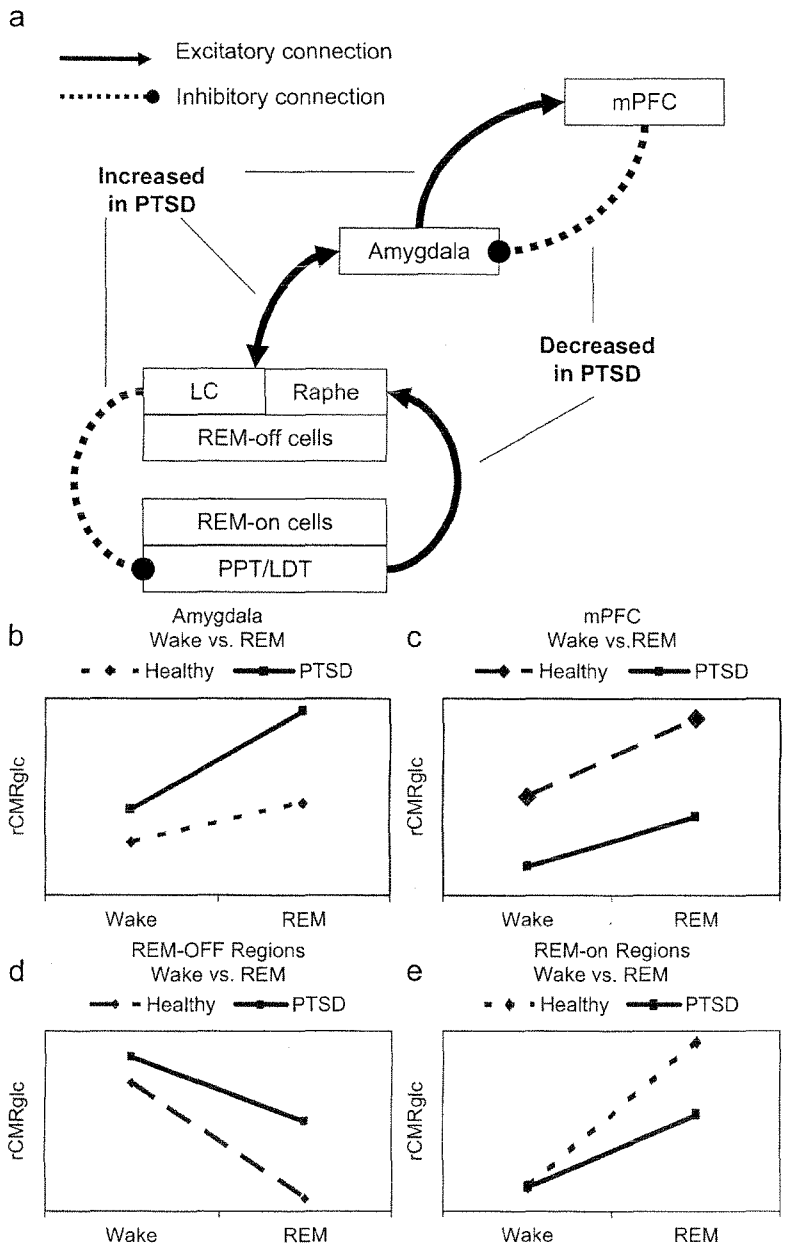

Figure 1 Proposed neurobiological model and correlates of PTSD during REM sleep. (a) Proposed neurobiological model of PTSD during REM sleep. mPFC: medial prefrontal cortex; LC: locus coeruleus; PPT: pedunculopontine tegmentum; LDT: laterodorsal tegmentum. (b–e) Relative to wakefulness, PTSD patients (black line) will show increased relative regional cerebral metabolic rate of glucose (rCMRglc) in the amygdala and brainstem REM-off regions, and decreased rCMRglc in the mPFC and brainstem REM-opn regions completed to healthy subjects (dashed lines).

and raphe and related inhibition of the PPT and LDT would be expected in PTSD subjects, and may directly relate to REM sleep disruption.

During NREM sleep, we propose that the hyperactivity of the amygdala and attenuated activity of the medial prefrontal cortex contribute to heightened whole-brain neuronal activity. Specifically, these changes may maintain or increase activity in arousal-promoting brain centers, and reduce activity in sleep-promoting centers. The resulting pattern of persistent arousal could directly contribute to complaints of insomnia. Figure 2 depicts the preliminary NREM sleep model and hypotheses regarding neurobiological correlates of NREM sleep relative to wakefulness in PTSD patients compared to healthy subjects. Specifically, it is hypothesized that the relative persistence of amygdala activity (Figure 2b) and blunted activity of the medial prefrontal cortex (Figure 2c) during NREM sleep would be associated with less deactivation of brainstem and forebrain wakefulness-promoting areas (Figure 2d; LC, raphe, posterior hypothalamus,

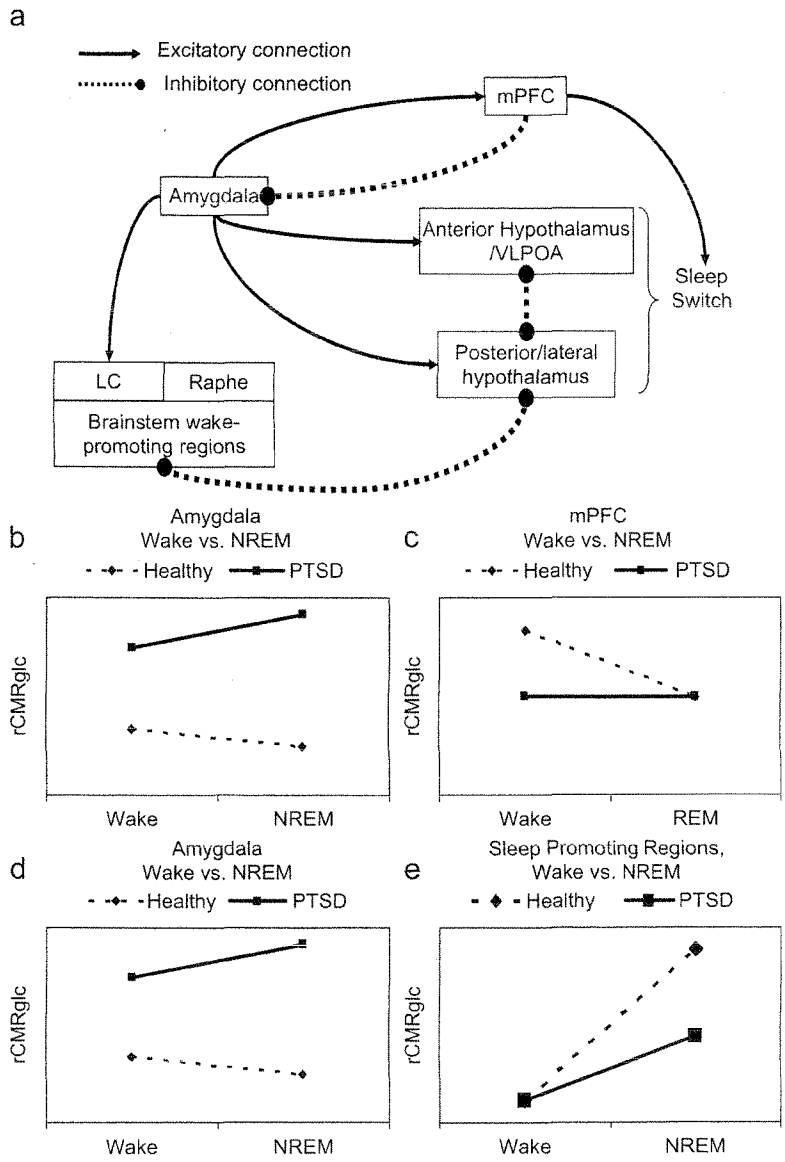

Figure 2 Proposed neurobiological model and correlates of PTSD during NREM sleep. (a) Proposed neurobiological model of PTSD during NREM sleep. mPFC: medial prefrontal cortex; LC: locus coeruleus; VLPOA: ventrolateral preoptic area. (b–e) Relative to wakefulness, PTSD patients (black lines) will show increased relative regional cerebral metabolic rate of glucose (rCMRglc) in the amygdala and wakefulness promoting brainstem and forebrain regions, and decreased rCMRglc in the mPFC and anterior hypothalamus compared to healthy subjects (dashed lines).

thalamus), and a blunted increase in activation of the anterior hypothalamus, and blunted activation in sleep-promoting regions (Figure 2e), such as the anterior hypothalamus (which includes the VLPOA) and solitary tract nucleus (although it may not be possible to directly observe changes in activity of small or diffuse nuclei given the limits of spatial resolution of current neuroimaging methods).

Discussion

PTSD is a prevalent disorder that is often resistant to recommended treatments, and is associated with enormous health care costs. Sleep disturbances are a core feature of PTSD that are often resistant to recommended first-line treatments, and independently contribute to poor clinical outcomes. The contribution of sleep disturbances to long-term health outcomes and costs in PTSD is not currently known, but is likely to be substantial. Emerging evidence suggests that sleep-specific mechanisms underlie the neurobiology of PTSD. However, the neurobiological underpinnings of PTSD, as it persists across the sleep–wake cycle, remain unexplored using sleep neuroimaging methods.

Sleep research in PTSD samples (as well as in other stress-related disorders such as acute stress disorder, adjustment disorders, prolonged grief disorder) is ripe for the broader use of state-of-the-science sleep neuroimaging methods required to identify the sleep-specific neurobiological underpinnings of PTSD, the correlates of resistance to first-line PTSD treatments, the predictors of response to sleep-focused treatments, and the mechanisms that are normalized by effective sleep treatments.

Future research directions have direct clinical implications in PTSD and sleep research. For instance, little is known about the effects of sleep deprivation and disruption on fear conditioning and fear extinction in healthy human subjects and in patients with stress-related disorders. Understanding the sleep-specific mechanisms that may facilitate fear conditioning and/or impeded fear extinction may be especially important in samples where trauma exposure is a likely event, such as during military deployment, combat exposure, and all emergency responders. Further investigating the role of sleep in the consolidation of traumatic memories as well as in processing emotional and traumatic material also provides an ecologically valid paradigm to further expand cognitive neuroscience models of sleep and memory. More in-depth models of the sleep-specific pathophysiological and neurobiological underpinnings of the relationship between trauma exposure, sleep, and PTSD can also guide the development and refinement of innovative prevention and intervention strategies targeting sleep disturbances in trauma-exposed and PTSD samples. For instance, an in-depth understanding of the sleep-related brain mechanisms susceptible to disruption following trauma exposure and in PTSD may facilitate treatment optimization by combining treatments that restore affected neural networks, and/or that enhance compensatory mechanisms. Identifying sleep-specific markers of vulnerability and resilience to chronic, maladaptive stress response and of sleep-focused treatment response may create new venues to prevent PTSD in high-risk samples (e.g., combat veterans, emergency workers). Finally, the nature of sleep-specific predictors of treatment response or failure to first-line PTSD treatments, or the underpinnings of effective sleep-focused pharmacological or behavioral interventions have not yet been explored.

In summary, the study of the neurobiological correlates of PTSD during sleep by using state-of-the-science sleep neuroimaging methods opens multiple opportunities to identify the sleep-specific underpinnings of this pervasive disorder, which in turn can inform the development of evidence-based interventions that normalize the underpinnings of PTSD across the sleep–wake cycle.

Practice points

1. Sleep disturbances often develop into independent, comorbid sleep disorders in adults with PTSD.
2. Complaints of sleep disturbances in adults with PTSD contribute to mental and physical health outcomes, including exacerbation of daytime PTSD symptom severity, anxiety, depression, irritability, cognitive functioning, and disability. Sleep disturbances, and potentially their more distal consequences, can be significantly ameliorated with sleep-focused treatment.
3. A thorough evaluation of the nature and adverse impacts of sleep disturbances on daytime symptoms and overall functioning should be integral to PTSD evaluation.
4. Sleep disturbances comorbid to PTSD require targeted interventions.
5. Randomized controlled trials indicate that prazosin and nefazodone can effectively reduce nightmares and insomnia in PTSD.

Other pharmacological interventions such as cyproheptadine, trazodone, zaleplon, and zolpidem may also reduce nightmares and insomnia, but formal clinical trials are required to fully assess their efficacy, safety, and durability in military and civilian PTSD samples.

6. Behavioral interventions for PTSD-related sleep disturbances such as imagery rehearsal, and behavioral insomnia treatments have received most empirical evidence for efficacy to date in both military and civilian PTSD samples.

Research agenda

In order to further refine our understanding of the pathophysiology of PTSD during sleep and to translate these findings into clinical practice, we need to:

1. Employ available sleep neuroimaging techniques to identify and probe the pathophysiological and neurobiological underpinnings of PTSD across the sleep–wake cycle.
2. Investigate the neurophysiological and neurobiological mechanisms that underlie sleep-focused treatment response and resistance in PTSD patients.
3. Develop and test innovative pharmacological and cognitive–behavioral interventions that specifically target and normalize altered physiological and neurobiological systems that subserve sleep disturbances in PTSD.
4. Conduct mechanistic, longitudinal studies to assess the independent effects of sleep disturbances on health outcomes in PTSD.

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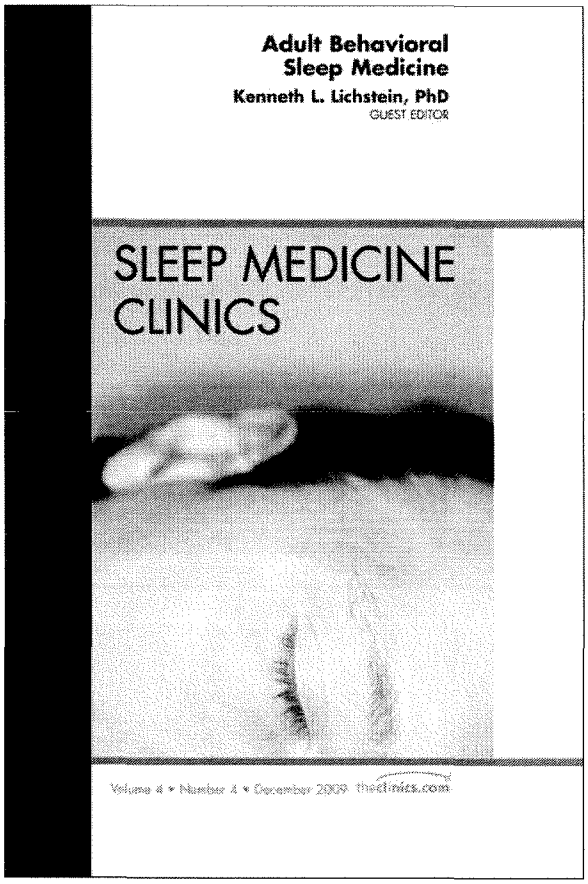

Correlates and Treatments of Nightmares in Adults

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KEYWORDS

• Nightmares • Sleep • Posttraumatic stress disorder
• Pharmacology • Cognitive-behavioral treatments

This article presents the definition of nightmares and diagnostic features, followed by a discussion on the prevalence and frequency of nightmares and related methodological issues. The potential etiologic factors of nightmares, associated features, and available pharmacologic and cognitive-behavioral treatment strategies are reviewed.

Current diagnostic classifications define nightmares as frightening dreams that awaken the sleeper. However, fear is not the only emotion reported in nightmares; and the importance of the awakening criterion for functional and sleep impairments associated with nightmares has been debated in the literature. These points are briefly summarized here. In this article, the term *nightmare* is broadly used to refer to disturbed dreaming that may or may not be accompanied by an awakening, and that is associated with clinically meaningful levels of daytime distress, functional impairments, or sleep disruption.

In reviewing available data on nightmare prevalence and frequency estimates, the need for more unified methodological approaches and longitudinal designs in future studies is highlighted. Although the literature is limited on the etiology of nightmares that occur outside the context of stress or traumatic responses, this article presents hypotheses previously suggested on the correlates and potential underlying mechanisms of nightmares. Selected associated features of nightmares (ie, psychopathology and sleep disturbances) are presented, and available and promising treatment strategies are described. Some pharmacologic and cognitive-behavioral treatments of nightmares have been shown to effectively reduce and eliminate nightmares, but few rigorous, randomized controlled clinical trials have been conducted. Finally, future directions for methodological consideration, research investigations, and clinical practice are offered.

DEFINITION

The Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR)[1] and the International Classification of Sleep Disorders, second edition (ICSD-II)[2] converge on defining nightmares as "intensely disturbing dreams that awaken the dreamer to a fully conscious state and generally occur in the latter half of the sleep period." However, these diagnostic classifications also differ on 2 key points. Firstly, they differ on whether nightmare-associated emotions are limited to fear and anxiety (DSM-IV-TR) or can include all dysphoric emotions, such as anger or despair (ICSD-II). Secondly, only the DSM-IV-TR specifies a criterion that the nightmare or resulting sleep disturbance is associated with significant distress or impairment in waking functioning.

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The expansion of nightmare-associated emotions beyond fear and anxiety is well recognized in the literature, although fear is the most commonly reported emotion in nightmares.[3] In contrast, the absence of a distress criterion in the ICSD-II has been criticized, because of evidence that distress is more important than frequency in determining whether nightmares are associated with negative outcomes, including sleep disturbance, psychopathology, or health behavior problems.[4]

The awakening criterion has stimulated significant controversy in the field. Historically, distressing dreams that do not lead to an immediate awakening (at least one that is remembered by the dreamer) have been labeled as bad dreams.[5] Theorists have suggested that dreaming serves an extinction function, and that the awakenings associated with nightmares, but not bad dreams, disrupts this extinction process.[4,6] Consequently, many studies dichotomize nightmares and bad dreams as distinct phenomena. However, evidence concerning the importance of awakening to associated distress or psychopathology remains mixed and raises questions about the clinical usefulness of this distinction. Specifically, available treatments to reduce unpleasant dreams usually focus on the extinction of distressing content, rather than on the extinction of these associated awakenings.

Some have argued that all dysphoric dreams fall on a continuum; in this view, nightmares are more intense than bad dreams, both being versions of the same basic phenomenon. Others support the view that the distinction between nightmares and bad dreams relates to underlying differences in the intensity of the emotional content.[7] However, findings from studies that have investigated differences in dream content intensity between nightmares and bad dreams show small differences between the 2 phenomena. For example, Blagrove and Haywood[8] reported that dreams judged to have caused awakenings were rated as more unpleasant (in line with nightmares as more intense versions of bad dreams). However, the statistically significant differences in emotion intensity ratings were less than 0.3 on a 7-point scale. A similarly small difference (approximately 0.7 on a 9-point scale) in ratings of emotional intensity in nightmares compared with bad dreams was also reported by Zadra and colleagues.[9] These small differences in dream intensity between nightmares and bad dreams suggest that dream intensity may not be the primary mechanism that distinguishes nightmares from bad dreams.

The reliability of patients' nocturnal awakening memories is another important, though minimally considered, aspect of the awakening criterion's clinical significance in defining nightmares. It is possible that bad dreams lead to much shorter awakenings, leading to amnesia of the arousal. For instance, awakenings less than 3 minutes in duration are often associated with retrograde and anterograde amnesia.[10] Blagrove and Haywood[8] attempted to address this concern by assessing the dreamers' subjective certainty about whether their disturbing dreams woke them up, and they found that participants were generally confident making this decision and particularly so when dreams were very unpleasant. Nevertheless, the lack of objective measures to accurately evaluate the duration of these awakenings makes it difficult to ascertain that bad dreams associated with an awakening are less subject to memory biases.

As indicated earlier, there is divergence between the diagnostic classifications of nightmare distress. Some have argued that nightmare-related distress is more clinically relevant than nightmare frequency to daytime functioning and psychopathology.[4] From this perspective, nightmares are viewed as a manifestation of the cross-state continuity of distress from waking to sleeping. In support of this assertion, distress is only weakly related to nightmare frequency,[11] but it may be more robustly associated with sleep disturbance[12] and measures of psychopathology[13,14] than with frequency. However, assessments of nightmare distress are vastly underrepresented in the literature,[4] being limited to 1 validated scale, the Nightmare Distress Scale,[11] which may potentially confound nightmare distress with nightmare frequency.[15] Again, longitudinal studies with reliable frequency and distress measures are necessary to fully evaluate the clinical significance of nightmare distress.

Neither classification system includes a criterion for the duration of the nightmare problem, perhaps because the cause of distressing nightmares is often undetermined, or because the clinical meaningfulness of duration of the nightmare problem has not yet been assessed empirically.

Nightmares should not be confused with other distressing nocturnal phenomena. Nightmares are most readily distinguished from other similarly distressing nocturnal events by the extent of mental content, the confusion or disorientation upon awakening, and the presence or absence of memory of the event on the following morning. Sleep recordings show that these distressing nocturnal episodes generally occur in different sleep stages. The particular treatments that are effective for each category of event also vary.

Sleep terrors are associated with intense autonomic arousal. They can begin with a piercing

scream, but they are paradoxically associated with difficulty in awakening the sleeper from the episode and in the sleeper returning to deep sleep after the episode.[2] In contrast, there is little confusion or disorientation upon awakening from nightmares, and episodes are vividly recalled the following morning. For sleep terrors, if the sleeper has any recall of the event, recollections the next morning are, at best, vague or fragmented descriptions of frightening images.[16] Although nightmares primarily originate in rapid eye movement (REM) sleep, sleep terrors occur in non-REM sleep, specifically the slow-wave sleep of stages 3 and 4.

In contrast to nightmares and sleep terrors, nocturnal panic attacks often occur in the first few hours of the night during the transition from light (stage 2) sleep to deep (stage 3) sleep. Intense arousal is inherent in nocturnal panic attacks, leading to abrupt and complete awakening from sleep in a state of panic, without an obvious trigger and usually without screaming; the panic attacks are associated with a difficulty in returning to sleep.[17] Complicating differential diagnosis is the co-occurrence that has been documented between these parasomnias, such as an association between monthly nightmares and an increased incidence of night terrors.[19] Although sleep terrors and nocturnal panic attacks share a common predisposing condition—sleep deprivation leads to an increased incidence of both[17,18]—the existing evidence suggests that nightmares lead to sleep disturbance rather than the reverse (see later discussion on association with sleep disturbance).

PREVALENCE AND FREQUENCY

Nightmares are most prevalent during childhood and young adulthood and decline thereafter.[4] However, prevalence estimates in the general population in all age ranges vary and overlap substantially. From childhood through to early adolescence, between 5% and 50% of children have nightmares, with the prevalence of nightmare "problems" generally falling into the 20% to 40% range. In comparison, up to 85% of adults report at least 1 nightmare within the previous year, 8% to 29% report monthly nightmares, and 2% to 6% report weekly nightmares.[19–21] The estimates of weekly prevalence of nightmares have proved consistent across cultures.[12,20–22] Similarly robust are findings of a lower prevalence of nightmares among the elderly, who report at levels 20% to 50% of that of young adults.[23–25]

The variability in estimates is due, in part, to differences in the criteria used, the definition of nightmares, the time frame of assessments, the emphasis on distress or nightmares as a "problem" across studies, and the type of informants (eg, patients, primary care physicians, parents). In studies of children, the information, generally gathered from mothers, may show underestimation in the prevalence of nightmares and may be confounded by the occurrence of other common childhood parasomnias, such as sleep terrors. Nightmare prevalence estimates are derived nearly entirely from cross-sectional data.

Sex differences in nightmare prevalence are one of the most consistent findings in the literature,[26] with a higher percentage of women reporting nightmares; unacknowledged exceptions do exist.[27] Researchers have offered various explanations that are not mutually exclusive for this difference: (1) self-report biases in women, (2) greater vulnerability to risk factors including abuse in women, (3) anxiety and mood disorders in women, (4) sex differences in coping styles, and (5) biologic differences in emotion processing.[4,11,28–30] Together, these findings highlight the need for conducting longitudinal studies using established diagnostic definitions, an important future step to establishing prevalence rates over the life span. Longitudinal studies would also provide new information on the potential modulators (eg, sex, coping styles, biologic factors) that may contribute to enhanced vulnerability or resilience to chronic nightmares. Although the developmental trajectory remains to be clarified, all estimates to date indicate that nightmares are a prevalent problem, underscoring the need for appropriate clinical identification, assessment, and treatment.

Data concerning the frequency of nightmares are also characterized by substantial variability, mostly because of differences in the assessment methods used across studies. Common methods to assess nightmare frequency are prospective nightmare logs or retrospective estimates of the number of nightmares that occurred over a predetermined period of time (usually 1 month to 1 year). Daily dream/nightmare logs that are completed on awakening in the morning can be a simple checklist or a more extensive dream diary used to record nightmare narratives.

Numerous studies have assessed nightmare frequency, using retrospective or prospective measures. The differences between retrospective and prospective methods affect frequency estimates. Specifically, retrospective estimates have yielded frequency estimates ranging from less than once per year to once per month,[27] whereas prospective measures have consistently provided

higher nightmare frequency estimates, particularly when compared with 1-year retrospective nightmare frequency measures.[27] Studies that have compared both assessment methods have reported that retrospective questionnaires underestimate nightmare frequency by a factor of 2.5 to 10.[7,13,31] Many of these studies have been conducted with undergraduates who are in their first semester of college, a time of social and emotional upheaval for many. The latter method may provide overestimates of nightmare frequency in noncollege populations. Differences in frequency estimates that are derived from retrospective and prospective measures are generally interpreted as indicating that retrospective measures underestimate nightmare prevalence. Monitoring of nightmares could potentially increase or decrease their frequency. Nevertheless, prospective nightmare measures have been recommended as the gold standard.[4,27]

The most sophisticated study on the topic evaluated the comparability of frequency estimates for nightmares and bad dreams, when assessed by 1-year and 1-month retrospective measures and by narrative and checklist prospective measures.[28] Including both types of prospective measures was intended to address the question of whether intensive monitoring (with narrative logs) results in higher frequencies than a less demanding approach (using checklist logs). In contrast to predictions, narrative logs produced lower nightmare frequency estimates than checklist logs that did not significantly differ from the 1-month retrospective measure and were possibly higher than the 1-year retrospective measure. When examining bad dreams, both prospective measures produced higher estimates than the retrospective measures, but the prospective and retrospective estimates for bad dreams were not significantly different from one another.

Attempts to assess nightmares via polysomnographic (PSG) recordings in the laboratory have been difficult, because nightmares tend to occur less frequently under these conditions.[32] Even posttraumatic nightmares (see the etiology section) have a low incidence (1%–10% vs up to 85% of nights) in the sleep laboratory relative to naturalistic conditions.[33,34] A pilot study, using ambulatory PSG recording, suggested that the presence of the PSG, rather than the setting, is the crucial factor in the lower observed frequency. In a sample of 12 inpatients in a psychiatric clinic, Spoormaker and colleagues (unpublished data, 2004) found a significantly lower nightmare incidence (8% vs 34.5%) using ambulatory PSG over two 24-hour recordings compared with daily logs over 7 days. However, the generalizability of this study outside of inpatient settings is uncertain, and PSG studies of nightmares remain too few to draw firm conclusions.

ETIOLOGY

Nightmares are associated with a range of psychiatric symptoms, full-blown psychiatric disorders such as posttraumatic stress disorder (PTSD), and sleep disturbances. Although some psychiatric, personality, sleep, and biologic correlates of nightmares have been described, most extant studies are cross-sectional, precluding conclusive determination of causality and etiology. Although longitudinal studies are awaited, findings suggest that traumatic events, waking psychological distress, or sleep disturbance may contribute to the onset and maintenance of nightmares. Some theories that have been offered on the etiology of nightmares are briefly summarized in the following sections.

Idiopathic Versus Posttraumatic Nightmares

An important etiologic distinction made to date is the difference between idiopathic and posttraumatic nightmares. Idiopathic nightmares refer to nightmares with unknown cause that are unrelated to a specific traumatic event or PTSD. Posttraumatic nightmares refer to dreaming disturbances that are part of the stress reaction following exposure to a traumatic event, either during the acute stress response or over the course of PTSD. Nightmares are a core feature of PTSD, with up to 90% of individuals with PTSD reporting disturbing dreams with some degree of resemblance to the actual traumatic event. Nightmares may occur as frequently as 6 nights a week in individuals with PTSD,[35] and they may continue for up to 40 to 50 years after the original trauma.[36,37]

The distinction between idiopathic and posttraumatic nightmares has not been firmly established in most of the literature available to date. Given the emerging evidence that persistent nightmares in the wake of a traumatic incident predict later posttraumatic symptoms,[38] making a differential diagnosis may be particularly important for early intervention to ward off PTSD. In addition, these 2 types of nightmares may differ in their associated sleep disturbance (see the following section on associated features) and in the timing of their occurrence during the sleep period. Further research is necessary to characterize fully the etiology, phenomenology, trajectory, and functional consequences of these ostensibly different categories of nightmares.

Nightmares Due to Thin Psychological Boundaries?

Hartmann and colleagues[39,40] proposed the constructs of "thin" and "thick" psychological boundaries to characterize chronic (idiopathic) nightmare sufferers versus those with little or no nightmare experience. Frequent nightmare sufferers tend to be more emotionally sensitive, open, and reactive to elements of their internal and external environments. Individuals with no nightmares, on the other hand, tend to be less reactive to internal and external influences. Several subsequent studies have reported positive findings on the relationship between clinical features of schizophrenia-spectrum disorders and nightmare frequency.[41,42]

Disturbance in a Generally Adaptive Process?

A prevailing assumption is that dreaming is adaptive,[43] and thus nightmares may constitute an anomaly in the adaptive process, also described as "a failed dream."[43] However, the evidence in support of this hypothesis is scant. Flanagan[44] suggested that sleeping, not dreaming per se, is an adaptive process. In contrast, it has also been suggested that nightmares themselves might be the adaptive process. For example, Picchioni and colleagues[45] reported that nightmares are positively associated with waking attempts to cope with stress, suggesting that nightmares may serve a beneficial function. However, the absence of a direct assessment of successful outcomes of coping in this study makes it difficult, at best, to relate nightmares to functional outcomes. The potential specific role of nightmares in adapting to waking stressors and the specific conditions and mechanisms that contribute to successful or unsuccessful adaptation to stress through dreaming disturbances remain to be investigated.

Genetic Predisposition to Nightmares?

A single study has investigated the possible genetic contributions to nightmares. Using data from the Finnish Twin Cohort study, a nationwide questionnaire study that included 1298 monozygotic and 2419 dizygotic twins aged 33 to 60 years, Hublin and colleagues[46] found a genetic influence on nightmares that differed slightly between childhood and adult nightmares. Genetic effects accounted for an estimated 45% of the phenotypic variance in childhood and for an estimated 37% in adulthood. The odds ratios for associated psychiatric disorders also varied by age group; children most frequently experiencing nightmares were 3.67 times more likely to have a psychiatric disorder than those who never experienced nightmares, whereas adults with frequent nightmares had an odds ratio of 5.87. This suggests that nightmares during adulthood have a strong association with psychopathology. Again, these findings highlight the need for longitudinal studies to rigorously assess the moderators and predictors of the trajectory of nightmares and their clinical outcomes over time.

ASSOCIATED FEATURES

Nightmares are associated with sleep disturbance, but longitudinal studies are required to ascertain the directionality of this association. Sleep disruption as a consequence of nightmares is implicit in their definition, given the criterion of awakening to a fully conscious state. Empirical data bear this out, because frequent nightmares are associated with increased reports of sleep-onset and sleep-maintenance insomnia, more frequent nocturnal awakenings, and worse sleep quality.[21,26,47] Breathing problems (eg, asthma) and snoring are linked to idiopathic nightmares,[48] whereas an association with full-blown sleep apnea has been reported in posttraumatic nightmares.[49] Although longitudinal data are limited, 1 prospective study found that posttraumatic nightmares occurring 3 months after a motor vehicle accident were associated with current sleep-onset and sleep-maintenance problems and predicted sleep maintenance difficulties after 1 year.[50]

Objective indices of sleep disruption, as measured by PSG, suggest that idiopathic and posttraumatic nightmares have been associated with different effects on sleep. Although both nightmare types share an association with elevated numbers of periodic limb movements, posttraumatic nightmares are related to longer and more frequent awakenings[51] this relationship is a possible consequence of a lowered arousal threshold during sleep in PTSD,[52] although the evidence on this is mixed.[53] In addition, posttraumatic nightmares may occur earlier in the night than idiopathic nightmares,[54] but this was not replicated in a recent study.[51] Individuals with idiopathic and posttraumatic nightmares also did not differ on total sleeping time, sleep onset latency, slow-wave sleep, number of microarousals, or any of several REM-related parameters.[51]

Waking Disturbance and Psychopathology

Perhaps most relevant to clinical discussions of nightmares is their relationship to waking disturbance or psychopathology. In general, nightmares appear to be linked to a greater incidence of

mental complaints in healthy and clinical populations.

An important part of the nightmare literature has focused on the relationships between personality traits and nightmare frequency. The association between nightmares and anxiety has been most widely investigated. Modest associations between different measures of trait and state anxiety (eg, death anxiety scales, ego strength scales, manifest anxiety scales, and nightmare frequency assessed retrospectively) have been reported.[7,31,55–60] However, the association between nightmare frequency and anxiety is weakened when assessed with daily nightmare logs instead of retrospective questionnaires.[7,31] Nightmare-related distress, rather than nightmare frequency, seems to be more strongly related to anxiety.[13,14,31] In general, studies have consistently reported mild-to-moderate correlations between nightmare frequency and distress and general symptoms of anxiety, mood, somatization, and hostility.[7,13]

As mentioned previously, nightmares are a core feature of PTSD and may be implicated in the pathophysiology of the disorder. In addition, a pretrauma history of nightmares (possibly idiopathic nightmares) predicts the severity of PTSD.[61] PTSD-related nightmares are often resistant to first-line PTSD treatments, but they respond well to pharmacologic and cognitive-behavioral treatments (see the following section).

Nightmares have also been linked to suicidality. Cross-sectional studies have demonstrated an association between nightmares and both suicidal ideation[62,63] and actual suicide attempts[63]; nightmares were the only sleep variable associated with suicidality in a sample of suicide attempters, after controlling for Axis I disorders (including PTSD) and symptom intensity.[64] One prospective study found that nightmare frequency, per 1-month retrospective self-reports, was related to the risk of suicide, with a 57% higher risk among those reporting occasional nightmares and a 105% higher risk among those reporting frequent nightmares.[65] Although all of these studies were statistically controlled for possible confounding factors such as sex, depression, and insomnia, only 1 study was controlled for PTSD.[65] This is an important limitation because PTSD is also linked to suicidality.[66]

TREATMENTS

Most available pharmacologic and psychological literature on the treatments of nightmares is derived from case reports and clinical trials targeting nightmares occurring in the context of PTSD.[67] Although very few studies have evaluated the effects of these treatments on nightmares of unspecified causes, there is little evidence suggesting that different outcomes would be observed.

Pharmacologic Treatments of Nightmares

By far, the most common treatments of nightmares involve pharmacotherapy. There have been numerous open-label trials, with various agents for the treatment of nightmares. To date, the most effective of available treatments of PTSD-related nightmares is prazosin. Prazosin is an alpha1-noradrenergic antagonist, which is used nightly and associated with clinically meaningful improvements in nightmares, accompanied by reductions in other sleep disturbances and daytime PTSD symptoms. Placebo-controlled studies of prazosin have consistently reported positive effects on nightmares in military and civilian samples.[68–73] However, nightmares recur with prazosin discontinuation.

Several other pharmacologic approaches have also been used with mixed results. Tricyclic antidepressants and monoamine oxidase inhibitors were among the first agents tested for nightmares because of the suppressant effects on REM sleep, but side effects and contraindications limit their clinical use. Selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, sertraline, and fluoxetine, are Food and Drug Administration (FDA)-approved as first-line recommended PTSD treatments, but their efficacy for nightmares is inconsistent across clinical trials. Trazodone and nefazodone, 2 serotonin-potentiating non-SSRI agents, have been associated with moderate-to-large beneficial effects on nightmares in open-label and controlled trials.[74–77]

Cyproheptadine, an antihistamine with serotonin receptor antagonist properties, has not been found effective for reducing PTSD-related nightmares in a randomized controlled study.[78,79] Similarly, guanfacine, an alpha2-adrenergic receptor agonist, was not found to be effective in reducing nightmares in patients with PTSD in 2 randomized controlled trials.[80,81]

Benzodiazepines are often prescribed to patients with PTSD, possibly as agents to manage sleep disturbances,[82–84] despite lack of evidence as to their effectiveness. Two randomized controlled trials found no support for the efficacy of benzodiazepines as treatment for nightmares in PTSD.[85,86] Although benzodiazepines can reduce nightmares associated with REM sleep behavior disorder,[87] their efficacy in alleviating nightmares from other causes is unknown.

Atypical antipsychotic drugs have also been tested in the treatment of PTSD-related nightmares in military veterans with PTSD. Studies conducted with risperidone, olanzapine and quetiapine have yielded mixed results.[88–90] Zolpidem (nonbenzodiazepine imidazopyridine[91]), gabapentin,[92] and mirtazapine[93] show some promise but await more rigorous evaluation.

Cognitive-behavioral Treatments of Nightmares

Cognitive-behavioral treatments of nightmares have focused on 2 general approaches. The first approach is derived from the literature and treatment methods for anxiety disorders. Specifically, desensitization is implemented with the use of repeated exposure to the fearful nightmare content and with habituation to the emotional response triggered by nightmare imagery. Three controlled studies[94–96] have assessed the efficacy of desensitization in reducing nightmare frequency, nightmare intensity, psychological symptoms (eg, anxiety, fear, depression, hostility, and general psychological distress), and sleep complaints. Although desensitization studies did not specify the cause of nightmares in patients enrolled in these trials, all have consistently reported improvements in nightmares and also in sleep disturbances and daytime symptoms of anxiety.[96] Desensitization studies that used nightmare recording or relaxation[94] as control treatment conditions also noted posttreatment improvements in nightmares. Improvements in nightmares were also found over the periods of follow-up assessments for patients randomized to the desensitization groups, which ranged from 1 to 7 months after treatment. Together, these studies suggest that desensitization can be an effective treatment for nightmares. The efficacy of desensitization for PTSD nightmares, however, has not yet been evaluated.

The second behavioral approach for the treatment of nightmares is imagery rehearsal therapy (IRT) and its variants. The goal of IRT is to decrease the frequency or intensity of nightmares by (1) repeatedly rehearsing (practicing) new dream scenarios during wakefulness, and (2) revising compensatory cognitions and behaviors that perpetuate nightmares. In comparison to desensitization, IRT does not involve exposure to distressing material. IRT emphasizes rescripting the original nightmare scenarios into new, nondistressing dream scenarios that are then mentally rehearsed several times per day. Exposure to the original nightmare scenarios is discouraged, and repeated sessions of mental rehearsal of new dream scenarios are implemented daily, 1 to 3 times per day. Generally, the instructions on how to create new dream scenarios are minimal. Patients may choose to alter the ending of the dream, to change specific elements of the original content (eg, characters, nature of interpersonal and social interactions), or to create an entirely new dream scenario.

A series of controlled studies showed that rescripting and mentally rehearsing new dream scenarios alone, with limited to no exposure to the distressing dream content or intense emotional reactions, can significantly alleviate idiopathic nightmares and PTSD-related nightmares, in patients reporting at least 1 nightmare per week[98] and sleep complaints.[47,98] A large controlled trial, involving sexual assault survivors with trauma-related nightmares, replicated these findings when compared with women assigned to a wait-list control group, by showing clinically meaningful improvements in nightmare frequency, reduced severity of daytime PTSD symptoms, and improved sleep quality.[99]

A variant of IRT, called Exposure, Relaxation, and Rescripting Therapy (ERRT[100]), has also been associated with long-term improvements in nightmare frequency, depression-symptom severity, PTSD-symptom severity, and sleep quality for trauma-related nightmares, compared with effects observed in a wait-list control group. ERRT is a combination of (1) education about trauma, PTSD, and sleep; (2) exposure to the nightmare content and distressing themes; (3) diaphragmatic breathing and daily progressive muscle relaxation; and (4) rescripting of the nightmare scenario guided by the therapists and other members of the treatment group. Contrary to IRT, ERRT encourages exposure to the distressing nightmare content. Future research is awaited to determine which patients to treat and how much exposure should be given in the treatment of nightmares.

To date, IRT has shown efficacy with PTSD and non-PTSD related nightmares[97,98,101,102] in civilian and military samples.[99,103] However, to fully evaluate and compare the efficacy of different cognitive-behavioral techniques for the treatment of nightmares, more stringent control treatment conditions and direct comparisons between IRT approaches and desensitization or exposure are required.

Other psychological approaches have also been used in the treatment of nightmares. For instance, positive case reports and case series are available in the literature for lucid dreaming,[104] hypnosis,[105] eye movement desensitization and reprocessing,[106] and psychodynamic therapy.[107,108] These approaches await controlled clinical trials to determine efficacy for nightmares and the related

impact of sleep disturbances and daytime functional impairments and distress.

SUMMARY

Nightmares, a common experience for most of the general population, are even more prevalent and frequent among clinical populations. This increased prevalence is consistent with converging evidence of their potential clinical significance across diagnostic categories. Accumulating evidence links nightmares to waking distress and psychopathology; prospective studies suggest that nightmares may be a risk factor for PTSD and increased suicidality, offering new venues for prevention and interventions.

Methodological limitations and differences, across studies to date, preclude a more complete understanding of many aspects of this fascinating phenomenon. Thus, more rigorous methods are needed to address numerous areas. Firstly, the variability in assessment methods may have led to imprecise prevalence estimates, and this limits our ability to compare findings across studies. Studies of nightmares under controlled laboratory conditions may provide novel insights into the psychophysiological correlates of these nocturnal events; however, multi-night designs, with larger samples studied under ecologically valid conditions, are required to accurately evaluate the frequency and prevalence of nightmares in the general population and in clinical samples. Such studies would also permit assessments of the relationships between nightmare distress and frequency. Secondly, many questions remain regarding the cause and outcomes of nightmares. Most findings concerning nightmares and waking function are limited to correlations based on cross-sectional observational data. Experimental and longitudinal designs are required to address questions around the relationships between nightmares, sleep disturbance, and psychopathology. Even in the case of posttraumatic nightmares, where a clear event precedes the onset of nightmares, little is known about the biopsychosocial pathways through which the trauma exposure affects dreaming. More randomized controlled studies are necessary (1) to evaluate and compare available and promising treatment strategies and (2) to establish guidelines and algorithms to guide clinicians in the treatment of nightmares. Effective nightmare treatments can be used as probes to test specific hypotheses regarding the psychophysiological mechanisms underlying nightmares.

A small contingent of highly dedicated scientists is responsible for the laudable advancements in the nightmare literature to date. These researchers have also posited some compelling hypotheses that deserve more rigorous testing. Opportunities for novel contributions to and advancement of this important area of clinical investigation await the efforts of the broader research community.

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Efficacy of Sleep Intervention in Military Veterans with Post-Deployment Adjustment Disorders

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BACKGROUND: Chronic insomnia and nightmares are prevalent in combat-exposed military veterans who experience post-deployment adjustment difficulties, including posttraumatic stress disorder (PTSD). The objective of this ongoing clinical trial is to evaluate and compare the efficacy and durability of prazosin (PRZ) and a behavioral sleep intervention (BSI) targeting insomnia and nightmares on primary sleep outcomes, and secondary outcomes of daytime symptoms compared to placebo (PBO). Preliminary findings on the acute effects of treatments on sleep disturbances are reported here. Exploratory data analysis has also been conducted to evaluate the nature of objective sleep disturbances in military veterans (n = 44; Mean age: 38.0 $\pm$ 11.9; 38 men, 6 women) who do (n = 25) or do not (n = 19) meet full diagnostic criteria for PTSD in comparison to age- and gender matched good sleepers (n = 24, Mean age: 41.4 $\pm$ 12.7; 18 men and 6 women).

METHODS: Military veterans with chronic sleep disturbances in a 1:1:1 manner to PRZ, BSI, or PBO. Treatments are administered weekly, over an 8-week period. Primary outcomes presented here include (1) Sleep Quality as determined by the global scores on the Pittsburgh Sleep Quality Index (PSQI) and PSQI Addendum for PTSD (PSQI-A). Secondary outcomes include daytime PTSD and depression symptom severity.

RESULTS TO DATE: We have consented 102 military veterans, and 48 remained eligible after completing screening procedures. 46 completed baseline assessments and were randomized to PRZ (n = 13), BSI (n = 14), or PBO (n = 15). We are currently blind to the randomization of 4 participants. Pre- to post-treatment, participants randomized to BSI showed greater improvements compared to the PBO and PRZ groups. Both BSI and PRZ showed marked decreased in PSQI-A scores compared to PBO. Sleep diary measures of sleep latency showed greater improvements post-treatment in the BSI group compared to the PRZ group. Wake time after sleep onset and sleep efficiency also showed greater improvements in the BSI and PRZ groups compared to PBO. Daytime symptoms of PTSD and depression were also significantly improved in the two active treatment groups. Compared to age- and gender-matched good sleepers, military veterans endorsed significantly poorer subjective sleep quality as measured by the PSQI compared to good sleepers ($p < 0.001$), and showed objective evidence of sleep disruption, as indicated by increased sleep latency and increased % stage 2 sleep, lower sleep efficiency, and decreased total sleep time slow wave sleep (all $p < .05$). Quantitative power spectral EEG analyses during NREM sleep showed greater cortical arousal (as measured by beta activity) and decreased sleep depth (as measured by delta power) in military veterans compared to good sleepers. PTSD status had minimal effects on objective measures of sleep disturbances.

CONCLUSIONS: PRZ and BSI appear to be associated with improvements in sleep and daytime measures compared to PBO. Compared to good sleepers, military veterans show objective evidence of sleep disruption that corroborate subjective sleep assessments. Clinically significant sleep disturbances affecting military veterans are responsive to treatments, and are associated with improvements in daytime symptoms.

IMPACT: Findings for this study will directly inform the development of effective treatment strategies targeting acute and chronic stress-related sleep disturbances in military samples.

Abstract:

Title: Quantitative EEG analysis in REM sleep in OEF/OIF combat veterans with and without PTSD.

Authors: Daniel Cohen, Jennie Alman, David Cashmere, Jean Miewald, Anne Germain

Introduction

REM sleep disturbances have been associated with Posttraumatic Stress Disorder (PTSD), but PSG studies have yielded inconsistent findings. In this study, we used quantitative EEG (qEEG) to compare beta activity (16-32Hz) as a measure of central arousal during REM sleep in combat-exposed veterans with and without PTSD. We hypothesized that PTSD would be associated with greater beta activity.

Methods:

Participants were combat veterans of Operations Enduring/Iraqi Freedom (OEF/OIF) drawn from an ongoing clinical trial. Assessments included 2 PSG nights, and questionnaires on sleep quality and psychiatric symptoms. Participants using psychotropic medications were excluded from this analysis. The second PSG night was used for qEEG analysis. Artifacts were rejected in 4-second epochs using an automated algorithm for EMG-twitches, and manually to remove eye-movement and pulse artifacts. Artifact-free REM epochs were subjected to spectral analysis using a fast Fourier transform model. T-tests were used to compare groups. Spearman correlations were performed between beta activity and clinical variables.

Results:
No group differences were observed on PSG measures. The number of 4-second REM epochs rejected for qEEG analysis did not differ between groups. The PTSD group showed lower beta activity in REM sleep than the non-PTSD-group (mean (SD): 0.060 (0.02) vs. 0.096 (0.03), p=0.013). No differences were observed in other qEEG activity bands. In the combined sample, REM beta activity was negatively correlated to PTSD symptom severity (rho=-0.52, p=0.04), PTSD avoidance symptoms (rho=-0.57, p=0.02), but not to hyperarousal symptoms (rho=-0.09, p=0.75).

Discussion:

Contrary to our hypothesis, beta activity was lower during REM sleep in combat veterans with PTSD compared to those without PTSD, and was not related to hyperarousal symptom severity. This small study raises the possibility of a complex, non-linear link between central hyperarousal, REM sleep, and PTSD symptom severity.

Research supported by: This research was supported by the National Institutes of Health (MH053035; MH024652; MH66227; RR024153; R21MH083035-01) and the Department of Defense (PR054093-W81XWH-07-PTSD-IIRA and PT073961-W81XWH-07-PTSD-IIRA).

A. Title: Waking qEEG in veterans with PTSD compared with subjects with insomnia and good sleeper controls.

B. Authors and Institutions: Jennifer Alman, David Cashmere, Robert Seres, Jean Miewald, Daniel J. Buysse, and Anne Germain

Introduction: Increased central nervous system arousal prior to sleep may contribute to sleep difficulties in patients with Posttraumatic Stress Disorder (PTSD) or Primary Insomnia (PI). Fast-frequency quantitative EEG (qEEG) activity (sigma: 12-16 Hz; beta: 16-32Hz) during waking EEG, a potential indicator of this arousal, was compared in patients with PTSD, PI, and Good Sleeper (GS). We hypothesized that both patients groups would show increased fast-frequency activity during evening wakefulness compared to GS. The relationships between qEEG measures, PSG sleep measures, and symptoms of PTSD, depression, and anxiety in the PTSD group were also explored.

Methods: Ten military veterans with PTSD (mean 37.6 ± 11.7 years old), 10 PI subjects (mean 35.3 ± 9. 7 years old) and 8 GSC (mean 40.1 ± 22.8 years old) were included in this study. PI and GSC were free of medications, medical conditions, psychiatric disorders and other sleep disorders. Six of the 10 PTSD subjects were medication free. Automated and visual artifact rejection were conducted on 5-minute waking EEG samples recorded within 2 hours of participants' habitual bedtime using FFT. Non-parametric Kruskal-Wallis tests and Spearman's rho correlations were conducted.

Results: There was no significant group difference in absolute or relative power for sigma or beta activity bands. In PTSD subjects, absolute beta power during waking EEG was significantly and positively correlated with the severity of PTSD, depression, and anxiety symptoms were (all $p < 0.05$), but not with PSG sleep measures.

Conclusion: In this sample, PTSD and PI subjects did not show greater indices of EEG arousal during evening wakefulness compared to GS. Increased fast-frequency activity during pre-sleep wakefulness was positively associated clinical symptom severity in subjects with PTSD. Previously-described changes in qEEG during sleep in PTSD and PI may suggest a state-dependent form of electrophysiological arousal.

Support: This study was supported by the US Department of Defense (W81XWH-06-1-0257) and National Institutes of Health (RR 00052, RR 024153, MH24652)

Attachment anxiety is an independent correlate of slow-wave sleep in military veterans with post-traumatic stress disorder

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Introduction: Sleep and interpersonal problems are highly prevalent in military veterans with PTSD and are associated with substantial comorbidities and increased healthcare costs. Cognitive vigilance and physiological hyperarousal have been implicated in stress-related sleep disturbances and are also related to anxious interpersonal styles. Attachment anxiety (a tendency to worry about the physical and emotional availability of close relationships) has been linked with poorer depth and quality of sleep in non-PTSD populations. This is the first study to examine the association between attachment anxiety and sleep in the context of PTSD.

Methods: Participants were 42 military veterans (85% male) with PTSD who were enrolled in a treatment study of sleep disturbances and PTSD symptoms. Data were collected at pre-treatment baseline. Attachment anxiety was characterized via self-report. Sleep outcomes included: subjective sleep quality, and visually scored total sleep time (TST), percentage of Stage 3 + 4 sleep, and rapid eye movement (REM) sleep, averaged from 2 nights of in-laboratory polysomnography. Given previous research on psychosocial stress and quantitative EEG parameters, we also examined delta and beta power during NREM sleep. Linear regressions evaluated the independent relationship between attachment anxiety and sleep after statistically adjusting for age, gender, marital status, PTSD symptom severity, and depressive symptoms.

Results: Greater attachment anxiety was associated with lesser slow-wave sleep, as assessed by the percentage of Stage 3+4 sleep (β = -.33, p = .03) and by absolute delta power (β = -.35, p =.006). Attachment anxiety was also associated with greater relative beta power (β =.37, p = .02) — an indicator of hyperarousal.

Conclusion: Anxiously attached individuals may be particularly vulnerable to stress-related sleep disturbances and stress-related illness in general, due to physiological and psychological hyperarousal which persists through the day and night.

Brief Behavioral Treatment for Chronic Insomnia in Combat-Exposed Veterans: Preliminary Findings on Acceptability, Barriers to Adherence, and Outcomes

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Introduction: Insomnia is one of the most common reasons for referral to mental health services in active duty personnel. Insomnia comorbid with post-deployment adjustment disorders is often resistant to the usual first-line pharmacological and psychological treatments for posttraumatic stress disorder (PTSD) and mood disorders. Behavioral treatments of insomnia have been shown to be effective. They are typically delivered over an 8-week period by experts in behavioral sleep medicine. However, behavioral treatments of insomnia have not been adapted and tested in military veterans with chronic insomnia comorbid with combat-related mental disorders and stress reactions. In addition, the format and expertise required to deliver behavioral treatments of insomnia in their current format may not be easily exportable and accessible in primary and community care settings where military returnees and veterans with diverse combat-related mental disorders and stress reactions often seek help. The goal of this ongoing study is to adapt and to evaluate the acceptability of a brief treatment that targets chronic insomnia in combat exposed veterans. We call this intervention Brief Behavioral Treatment of Insomnia for Military Veterans (BBTI-MV).

Methods: BBTI-MV is a manualized treatment adapted from a brief behavioral interventions developed to chronic insomnia in older adults over the course of an NIA-funded study (AG00972; PI: Buysse). The treatment consists of 2 face-to-face sessions, and 2 telephone contacts over a period of 4 weeks. Participants receive a workbook with summary slides for each component discussed during the treatment sessions. The first session (week 1) involves education about sleep and insomnia, and then focuses on tailoring instructions for sleep restriction and stimulus control to each participant. The second face-to-face session (week 3) focuses on the review of progress and obstacles to adherence, by using prospective sleep diary and actigraphy data returned by participants each week. Instructions for modifying the participant's sleep schedules are also provided. On weeks 2 and 4, a telephone contact is conducted to verify and encourage adherence to treatment recommendations, evaluate side effects, and make adjustments to the recommended sleep schedule if necessary.

To date, 13 combat exposed military veterans (n =12 men, 1 woman) between the ages of 22 and 66 years old have been recruited via public advertisement and provided written, informed consent. Participants completed structured diagnostic interviews for past and current psychiatric history including PTSD, sleep and medical disorders. Participants are included if they were exposed to combat, report at least moderate symptoms of insomnia as indicated by a score $\geq$ 15 on the Insomnia Severity Index, and are psychiatrically and medically stable. All complete a sleep 7-night diary daily over the course of the intervention. They are also requested to wear an actigraph during the duration of the study to evaluate adherence to recommended sleep wake schedule. Side effects are assessed with the Asberg Side Effect Scale modified for the cognitive-behavioral interventions. Self-report measures of insomnia symptom severity and overall sleep quality are assessed using the Insomnia Severity Index (ISI) and the Pittsburgh Sleep Quality Index (PSQI) pre- and post-intervention.

Results: Of the 13 participants enrolled to date, five have completed BBTI-MV; two withdrew prior to initiating treatment because of improvements in sleep associated with changes in work/family schedules; four endorsed symptoms consistent with sleep apnea and were referred for further evaluation; and two are currently receiving treatment. Participants who completed treatment high satisfaction with the intervention and therapist, and rated the intervention as credible and acceptable. Few barriers to adherence were reported, and included difficulty complying with the recommended sleep-schedule on week-ends when military training drills are held, and lack of motivation to get out of bed on weeks-ends or days where no morning activities are planned. Post-treatment, 3 completers showed clinically meaningful improvements in insomnia and overall sleep quality as indicated by a decrease of at least one severity category on the ISI, and a decrease of 3 points on the PSQI. The other 2 completers showed some improvements in insomnia complaints and sleep quality, but did not achieve criteria for clinically meaningful improvements.

Conclusion: These preliminary case studies suggest that BBTI-MV may be associated with significant improvements in sleep in military veterans with chronic insomnia. Participants rated the intervention as acceptable and credible. Motivational interviewing techniques may be helpful to enhance adherence and optimize short term outcomes. Brief behavioral treatments for chronic insomnia comorbid with post-deployment adjustment disorders may be effective as a first-line adjunct intervention in returning veterans.

Support: This study was supported by the US Department of Defense W81XWH-06-1-0257.

Brief Behavioral Treatment for Insomnia in Military Veterans: Preliminary Findings

Introduction: Chronic comorbid insomnia is prevalent in military veterans. This pilot study aimed at adapting a brief treatment for insomnia (BBTI) in combat-exposed military veterans (MV) and evaluating its credibility, acceptability, adherence, and possible therapeutic effects.

Methods: Twenty military veterans (19 men, Age: 54.3±14.7 years old) enrolled in this study. Visual analog scales were used to assess treatment credibility, acceptability and satisfaction with BBTI. Veterans completed the Insomnia Severity Index (ISI) and the Pittsburgh Sleep Quality (PSQI) pre- and post-BBTI. BBTI was delivered over 2 face-to-face sessions, and 2 brief telephone contacts over a period of 4 weeks. Session 1 focuses on education and on tailoring instructions for sleep restriction and stimulus control to each participant. On subsequent weeks, contacts focused on the review of progress and obstacles to adherence, using prospective sleep diary and actigraphy data.

Results: Eleven veterans initiated and completed BBTI. Nine were unable to start BBTI-MV due to family/work obligations. Chronic insomnia was comorbid with subthreshold or full criteria for posttraumatic stress disorder (n=6), other anxiety disorders (n=5), and/or depression (n=1). Pre-BBTI, treatment expectations reflected some skepticism, but were generally positive. Veterans attributed high credibility (70% ± 22%) to BBTI and high satisfaction (98%) with BBTI. Few barriers to adherence were encountered, and 98% of sessions were completed. Post-BBTI, 5 veterans showed a reduction ≥ 6 points on the ISI, and 8 showed a reduction by ≥ than 3 points on the PSQI. Four of the eleven veterans achieved ISI and PSQI scores below clinical thresholds post-BBTI.

Conclusion: These data suggest that BBTI may be associated with significant improvements in chronic insomnia in military veterans. BBTI is acceptable, credible, and associated with high levels of satisfaction. BBTI may be a helpful first-line adjunct intervention in returning veterans with insomnia comorbid who experience post-deployment adjustment difficulties.

Support: This study was supported by the US Department of Defense (W81XWH-06-1-0257), and the National Institutes of Health (AG00972; MH080696)

Sleep Disturbances in Military Veterans with Post-Deployment Stress Disorders: From Neurobiology to Treatments

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Stress-related sleep disturbances are the most common reason for referral to mental health services in active duty military personnel. Nightmares and insomnia are core features of posttraumatic stress disorder (PTSD). PTSD is characterized by symptoms of re-experiencing, avoidance, and hyperarousal that persist for more than one month after exposure to an event that involves threat to integrity of the self or others accompanied by intense fear, helplessness, or horror. Recent estimates indicate that approximately 20% of returning military service members deployed to combat theaters suffer from PTSD.

Nightmares, insomnia, and other sleep-disrupting nocturnal behaviors are commonly reported in individuals with PTSD, and independently contribute to poor clinical outcomes. There is growing evidence that sleep disturbances occurring early after exposure to trauma increase the risk of PTSD, whereas the persistence of consolidated sleep post-trauma exposure increases resiliency. Sleep disturbances are often resistant to first-line treatments of PTSD recommended by clinical guidelines. Instead, psychological and pharmacological treatments that specifically target sleep are often necessary, and improvements in sleep symptoms are accompanied by clinically meaningful improvements in daytime symptoms of PTSD, depression, and anxiety. Together, these observations suggest that sleep disturbances contribute to the pathophysiology of PTSD, and that normalization of sleep contribute to recovery. Thus, investigating the neurobiology of PTSD during sleep can provide novel insights into the development of effective treatments that target and normalize abnormal brain function across the sleep-wake cycle. More broadly, understanding the pathophysiology and developing effective treatments of sleep disturbances comorbid with PTSD can guide therapeutic efforts for sleep disturbances occurring in the context of other stress-related psychiatric disorders, such as major depression and prolonged grief disorder. In this presentation, Dr. Germain will discuss findings on the pathophysiology of PTSD during sleep and a sleep-focused neurobiological model of PTSD guiding new neuroimaging studies. Results from clinical trials aimed at testing and comparing cognitive-behavioral and pharmacological treatments targeting nightmares and insomnia in military veterans with PTSD will be presented.

APPENDIX F

PERSONNEL COVERED ON THIS AWARD

PERSONNEL COVERED ON THIS AWARD

Principal Investigator: Anne Germain, Ph.D., Associate Professor of Psychiatry. 25% effort. She assumes primary responsibility for scientific leadership and administration of this research study.

Co-Principal Investigator: Eric A. Nofzinger, M.D., Professor of Psychiatry. 7.5 % effort. Dr. Nofzinger is a staff physician at the Pittsburgh VA University Drive Sleep Disorder Center. In addition to his clinical expertise in sleep medicine, Dr. Nofzinger is an expert in the area of sleep research in clinical samples. His served as the un-blind clinician on the study, and as such reviewed clinical data for each patient each week, and with the research pharmacist, determined whether to maintain, increase, or decrease medication doses based on the clinical response and side effects. Dr. Nofzinger did not draw salary support on this award from October 2009 until March 2010, as he was on entrepreneurial leave from the University. He, however, remained activity involved as an external consultant. His role was on the study was covered by Dr. Buysse, consultant on this study.

Study Physician: Douglas Moul, MD, Assistant Professor of Psychiatry (October 2006 to July 2008), and Oommen Mammen, MD, Assistant Professor of Psychiatry (July 2008 to March 2010): 10% effort. The study physician was responsible for all aspects related to prazosin/placebo administration and clinical management of participants randomized to the prazosin/placebo arms. The physician assistant assisted the research coordinator in the consent process, so that he was able to accurately address questions raised by the participants regarding medications and side effects or any other concerns related to medications. The physician acted as the blind physician in the treatment phase of the study.

Research Coordinator: Abdul Hakim, MSW (5/2006 to 5/2009) and Ryan Stocker, BA (5/2009 to 3/2010).
The Research Coordinator was responsible for recruiting and screening of potential study participants. When potential subjects were identified, the research coordinator conducted initial telephone screen to ascertain participants' eligibility into the study. The research coordinator was then responsible for obtaining informed consent from eligible subjects, collecting questionnaire data, and conducting psychiatric diagnostic interviews regarding sleep and mental health history. The research coordinator was also responsible for explaining study procedures to the participants, scheduling sleep studies, and coordinating necessary personnel, and conducting weekly telephone follow-ups with study participants. Finally, the research coordinator assisted the investigators in the preparation of reports and communications with the Institutional Review Board.

Research Therapist: Robin Richardson, LCSW. 25% effort. Mrs. Richardson was responsible for administering clinical rating scales, delivering the behavioral sleep

treatment, and for the clinical management of patients during the treatment phase of the study. Mrs. Richardson completed a departmental training program to ensure reliability in these assessments. During the treatment phase of the study, Mrs. Richardson met weekly with each patient to evaluate progress and side effects, and to ensure the proper collection of interim home and clinical evaluations (e.g., sleep diaries, CGI scales). Because was also blinded to treatment assignment, and conducted end-of-study ratings including structured interviews and ratings scales. Finally, she assisted the Study Coordinator in tasks related to recruitment and screening when necessary.

Data and data entry clerk: Noelle Rode. 30 % effort. Mrs. Rode is responsible for data entry, verification for clinical and sleep data, development, maintenance, and documentation of databases for the clinical and sleep, weekly production of recruitment and clinical reports for the total sample and well as for individual participants.

Psychopharmacology Lab technician: Denise Sorisio: 10% effort. Mrs. Sorisio is responsible for processing blood samples, performing the HPLC analysis of prazosin and providing the drug concentration data to the principal investigator.

Statistician: Amy Begley, MS. 10% 10% effort. Ms. Begley is responsible for data modeling and conducted statistical analyses.

Polysomnographic Technicians II: Karen Quigley, B.A., RPGST. 30% effort. Mrs Quigley's responsibilities include visual scoring of EEG sleep, apnea, movements, EKG arrhythmias, and microarousals, and maintenance and preparation of equipment and material necessary for sleep studies.

Quality Assurance Specialist: David Cashmere, B.Sc. 20% effort. Mr. Cashmere serves a number of roles related to accurate collection, data pre-processing, and documentation of EEG sleep and EKG signal collected during sleep studies. He also serves as the contact for commercial vendors and technical personnel in programming and maintaining software and hardware systems employed for in-home sleep studies.